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MILITARY MEDICINE: THE OLD AND THE NEW*

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PROGRESS, whether it be natural, political, or scientific, rarely proceeds long at a uniform rate. The unceasing effects of erosion and climatic cycles on the earth's surface are interspersed with earthquakes, volcanic eruptions, and other cataclysmic events that accomplish in minutes or hours changes ordinarily requiring centuries or possibly millions of years. Armed invasions effect political changes that otherwise would require generations or possibly not occur at all. Likewise in the fields of science, war is a force that quickens progress to an enormous degree. Nowhere is this effect better represented than in the science of medicine.

No branch of medicine has escaped the high tempo of the period. Preventive medicine, therapy, research, medical education, and even the doctor-society relationship are being rapidly molded to new forms. Quite in contrast to conditions existing at the beginning of the first World War, anticipation of the present conflict found many current trends well under way prior to Pearl Harbor.

In the field of preventive medicine great strides have taken place. As examples one may mention the immunization of all military personnel against tetanus, the routine roentgenographic examinations of the chest of individuals entering the armed services, and the establishment of the Board for the Study of Influenza and Other Epidemic Diseases in the Army. A score of others could be cited.

Tetanus, one of our most feared complications of battle injuries during the conflict of 1917–1918, is practically nonexistent in our overseas hospitals today. Moreover, our soldiers are spared the discomfort and occasional anaphylactic reactions associated with the former routine prophylactic administration of tetanus antitoxin.

The roentgenographic study of the chests of all individuals entering the military service since the beginning of 1942, and of a very large majority

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prior to that time, has resulted in a tuberculosis incidence far below that recorded during World War I. It has also been the greatest case finding activity ever undertaken. Though intended primarily to exclude tuberculous individuals from the military forces, it has been the means of detecting early tuberculosis in thousands of men and women who, not suspecting the disease, otherwise would have permitted it to progress much to their detriment and the danger of their associates. Incidentally, it has proved the practicability of stereofluorophotoroentgenography through which mass tuberculosis surveys may be made far more economically and efficiently than ever before.

Profiting by the experiences of 1917–1918, measures were taken early in the current mobilization to anticipate the problems of acute infectious diseases, especially those of respiratory origin, and the Board for the Study of Influenza and Other Epidemic Diseases was formed. This board, acting as an advisory and coördinating body, set up commissions devoted to each of the more important infectious diseases. To fill in gaps in our knowledge of these conditions they organized numerous research studies in the field as well as the laboratory, and appointed regional groups to act as "trouble-shooters" at stations where actual or potential epidemics might appear. In this manner approximately 100 of the nation's outstanding epidemiologists and research workers in infectious diseases have been mobilized. One or more of these groups is constantly in the field studying and advising at points where the welfare of our soldiers is threatened with infections of various sorts. Recently this board has conducted an extensive survey of camps to determine the effects that may be anticipated from increasing the densities of military population therein. It is contemplated that as far as possible, epidemics will be *forestalled*, rather than stopped.

Constant progress is being made in the prevention of disease through prophylactic use of sulfonamides. Because of the caution which must attend the widespread employment of such potent remedies, they have been employed conservatively and only where the local situation appeared to warrant their trial. Fortunately, as yet no untoward results have appeared. There has been no evidence to indicate that either blood dyscrasias or sensitization to subsequent administration of sulfonamides results from occasional moderate dosage of these drugs for prophylactic purposes. Used in this way few individuals have evidenced idiosyncrasies, even temporary in nature, toward sulfonamides.

The most striking results have attended the administration of sulfathiazole as a prophylactic against gonorrhea and sulfadiazine or sulfathiazole to eradicate meningococcus carriers and control meningitis epidemics. For venereal prophylaxis use of sulfathiazole has been authorized only under well controlled conditions in bodies of troops with excessively high venereal rates, 100 cases per thousand per annum or higher. The reports are very favorable, and the only question that remains unsolved is the deleterious

effect that one must anticipate from the frequent use of sulfonamides in this manner by those who habitually expose themselves to venereal infections.

The occurrence of meningitis in the armed forces during the last few months has provided an excellent opportunity for using the sulfonamides prophylactically in this disease. Although the number of cases has been comparatively small, the carrier rate in some instances has been very high. In one large camp a carrier rate of 79 per cent was promptly reduced to less than 1 per cent by the administration to each individual of 6 grams of sulfadiazine. Though the carrier rate gradually increased to 16 per cent and 25 per cent after three and six weeks respectively, cases of clinical meningitis ceased to appear. Those of you who struggled through meningitis epidemics of the first World War will be relieved to know that we no longer feel it necessary to identify carriers by bacteriological methods and to hold them in working quarantine.

The development of measures for the prevention, suppression, and therapy of malaria has progressed beyond expectation. Thanks to the skill of our organic chemists atabrine has been synthesized in this country and is now being manufactured in enormous quantity. Intensive research is being directed to the development of other anti-malarial drugs, and we may anticipate new and more effective remedies in the not too distant future. The development of satisfactory insect repellants by the Bureau of Entomology of the Department of Agriculture in coöperation with the Medical Department has been a noteworthy accomplishment. It has been no easy matter to synthesize materials that would protect the jungle fighter from the ravages of mosquitoes and other insects and at the same time not have toxic or other objectionable features that would militate against their use.

Some concern has recently been expressed about the possible spread of malaria in the United States by soldiers returning from combat areas where the disease is hyperendemic. Though this is a problem which must be met, it is one that does not present insuperable difficulties. The factors that contribute to the spread of malaria are thoroughly understood and on the whole are being adequately met. Proof of this is found in the fact that the malaria rate for troops in this country was lower in 1942 than ever before, notwithstanding the fact that a large proportion of them were under training in the southern states where malaria is endemic. Some increase in the incidence of malaria may be anticipated, but with the knowledge and facilities that we possess I cannot for a moment entertain the thought that the people of the United States will ever be menaced by serious epidemics of the disease.

Throughout the centuries typhus has been recognized as the scourge of armies and war stricken peoples. The last World War and the post-war period were no exceptions, and when the history of the present conflict is recorded we shall undoubtedly find that the disease has again affected military campaigns and shaped the destiny of peoples impoverished by war. To

protect our fighting legions, new and more effective vaccines and other preventive measures are being employed. The use of a powder which, dusted in the seams of clothing, will kill lice and their eggs and yet have no toxic or irritating effect on the wearer, has done much to solve the "cootie" problem of 1918. Another valuable discovery is a gas which is innocuous to man but which will destroy lice, bed bugs, and other vermin and their eggs in infested clothing, bedding, and accoutrements. Though our soldiers are fighting in endemic typhus areas, it is anticipated that these measures will reduce the incidence to a minimum.

In the realm of therapy the picture has changed as materially as has that of preventive medicine since the days of World War I. Chemotherapy now provides agents for the treatment of many infections for which there were previously no specific remedies. They have largely replaced specific sera in the management of pneumonia, meningitis, and bacillary dysentery and local treatment in the therapy of gonococcus infections, all with marked reduction in the morbidity and mortality rates incident thereto.

The death rate from pneumococcus pneumonia has dropped markedly since the 1918–1919 era. Of course, all of these improvements cannot be attributed to sulfonamides though the prognosis has undoubtedly been improved greatly by their use. Another interesting observation is the reduced incidence of pneumococcus infections among civilian as well as military populations. One wonders if the extensive use of sulfonamides in other conditions as well as pneumonia has not lowered the carrier rate below a critical ratio at which pneumococcus infections are prone to develop.

In meningococcus meningitis the mortality rate under chemotherapeutic management is only one-fourth that of the first World War period. At the same time the patient is spared the distress of spinal punctures and the meningeal irritation attending the intraspinal administration of antisera. In gonococcus infections the days lost and the incidence of complications have been materially reduced by the use of sulfa drugs, and possibly, more to the point, by discontinuing the practice of intraurethral treatment. In bacillary diarrheas improved results are likewise the rule. Acute manifestations usually are promptly relieved by the administration of sulfaguanidine or other sulfonamides. Only in the severe Shiga type does antitoxin appear still to have a place in therapy.

In surgical practice equally striking changes have taken place. Technics have been developed for the successful treatment of conditions within the cranium, thorax, and abdomen which were considered hopeless only two decades ago. The age of industrialization and motor transportation has given physicians generally a greater experience in the care of traumatic conditions. Here also the sulfa drugs occupy an important place in the prevention and treatment of complicating infections. Immunization of our forces with tetanus toxoid appears to have practically eradicated tetanus as a complication of battle wounds. Among 1,252 casualties admitted to an

evacuation hospital during recent operations on Guadalcanal there were no cases of tetanus and only one of gas gangrene. Of 43 fatal cases only seven did not have wounds involving one or more of the major body cavities. The fact that there were only seven deaths from wounds of the face, neck, and extremities testifies to the low incidence of serious complicating infections. It should be noted that during the operations cited evacuation was through rugged tropical country with the wounded carried by hand for many miles at times. Trails had to be cut through jungle growth and on occasions it was necessary to string ropes along slippery muddy slopes to keep litter bearers from falling. Steps had to be fashioned in the sides of precipitous ravines to carry the wounded across, or overhead trolleys, arranged to transfer them from one valley bank to the other. On other occasions wounded men were ferried on improvised rafts down tropical streams and along the island coasts. Adding to the difficulties were Jap snipers who, passed by the battle line, remained hidden in the forest and fired on litter bearers carrying wounded men along the trail. Under such conditions of evacuation may we not justly take pride in the fact that the mortality rate in the evacuation hospital was less than 3½ per cent and that deaths resulted only from wounds of the most serious character?

This picture brings up a matter which I feel cannot be overemphasized, that is, the importance of the unit medical officer. To supervise the health of troops in our far flung combat areas and to accompany them into battle to render first aid, perform necessary emergency operations, and prepare them for transportation to the rear requires tact, courage, and judgment of superior degree. Nothing can contribute more materially to the morale and efficiency of troops than the successful battalion or regimental surgeon; neither is there a military assignment that will contribute more signally to the physician's success in civil life after the war.

Among the outstanding contributions to military surgery should be mentioned the drying and packaging of blood plasma and the development of intraspinal and intravenous anesthesia. Because of its ease of administration and smaller bulk pentothal-sodium has largely supplanted ether as a general anesthetic in forward medical installations. All of you are familiar with the Army and Navy plasma program. Generous amounts of dried plasma are now going to all theaters and the product is being used on every battle line with unfailing acclaim. In field, evacuation, and general hospitals, whole blood transfusions are freely used, the procedure being facilitated by routine typing of all military personnel, thereby necessitating at the time only cross matching to insure compatibility of the donor's blood and that of the recipient.

The elaborate evacuation and surgical hospitals operating closely behind more or less stabilized battle lines in the first World War have now given way to highly mobile and lightly equipped field installations. During recent fighting in New Guinea successful major surgery was done in hospitals the

entire equipment of which was transported on the backs of medical personnel and native carriers.

In aviation medicine we have a new and extensive field. Advances in airplane performance have brought forth many problems concerned with centrifugal force, rapid changes in altitude, and rarefied atmospheres, and their effects upon the human mechanism. Airplane evacuation has contributed greatly to the comfort and adequate care of our battle casualties. Thousands of our sick and wounded have been transported by air ambulance and transport plane from combat areas to fixed hospitals hundreds of miles to the rear. In the island warfare of the Southwest Pacific this means of evacuation has been particularly successful.

Research has grown apace. Though President Lincoln recognized its need during the Civil War and President Wilson further stimulated its progress at the time of World War I, no previous period has witnessed the extensive research activities that are now going on. In civilian institutions, in the Army, Navy, and Public Health Service, and under the sponsorship of the Committee on Medical Research of the Office of Scientific Research and Development, there is a program of medical research that has never been approached before. Though this is stimulated largely by the war effort, its character is such that medical science will feel its beneficial effect not only throughout the current struggle but also during the post-war period and the years following.

Medical education has witnessed changes of which none of us dreamed a few months ago. The importance of tropical medicine is now being recognized by the inclusion of courses in tropical medicine in the curricula of most Grade A medical schools. In the economic status of the physician and in his relationship to society and to the state we sense impending changes, the imminence and the magnitude of which, one whose life has been spent in military medicine should not venture to predict.

One could proceed ad infinitum citing advances in medical science since the days of our expeditionary force in France. Reverting, however, to the current period and to the phases of medicine that are more directly related to military operations, we may state quite positively that never before has progress been so rapid. New and unexpected problems are demanding prompt and daring solutions, and the magnitude of application is yielding experience that would ordinarily require decades to obtain. Though out of the fiery cauldron of war we will find much that is dross we will coincidentally realize advances in medical science that could be attained in no other way.

AVIATION MEDICINE*

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Twenty years ago, had I then had the honor of addressing the American College of Physicians on the subject of Aviation Medicine, I probably would have spent my allotted time profitably describing just what aviation medicine means. Today, however, such an explanation is unnecessary. The number of flight surgeons, the number of physicians who practice aviation medicine, has grown to such a degree as almost to parallel the growth of aviation itself, and the medical profession is now aware that aviation medicine exists. Particularly in the services, the specialty of aviation medicine, if you wish to term it that, is as well recognized as is any of the other specialties.

The statement that the specialty of aviation medicine is well known perhaps needs a little qualification. Very recently there came to my desk as medical officer in charge of the School of Aviation Medicine in Pensacola a letter from a medical officer of the Navy who claimed that he had requested a course in aviation medicine, which leads to the designation of Flight Surgeon, because he expected to get surgical training, and upon finding that the course did not include surgery, he requested that his name be withdrawn and that he be given other duty. It is difficult to imagine just what sort of surgery he expected to get. Perhaps he had ideas of being an ambulance surgeon of the air; but, in teaching aviation medicine, surgery is not included in the curriculum.

The particular topic concerning aviation medicine to be discussed is one which will be of interest to you as members of the American College of Physicians, since it will deal with aviation physiology and the results of oxygen want and low atmospheric pressures, namely, anoxia and aeroembolism, or bends. This is a timely topic, because anoxia and aeroembolism are not peculiarly military problems. The civilian pilot and passengers in civilian planes are just as vulnerable to the effects of anoxia and low pressures as are the crews of military airplanes. Flight surgeons have always been interested in the question of anoxia and its prevention, which is, of course, adequate oxygen supply. They have been interested in partial pressure, in alveolar pressure, and in the amount of oxygen tension necessary in the alveoli to provide proper arterial saturation.

But for a long time our efforts were combated by the old-time flier, who knew better than we because he had flown at heights at which we told him it was impossible for him to fly safely without oxygen.

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

In those days the stations were not equipped with low pressure chambers in any great numbers. Those that existed were for experimental purposes and were not available for indoctrination of personnel. It was the custom of most old-time pilots to describe to what extreme altitudes they had flown without oxygen, how well they had felt, how well they had done their flight jobs, and how well they had accomplished their missions. Those who had seen the results of anoxia realized that human limitations were unescapable realties, and knew that these men were not telling the truth. But it was a difficult matter for the flight surgeon, who might not be a pilot, to persuade other younger pilots that these old-timers were not telling the actual truth and were perhaps telling only what they believed to be true.

Not so many years ago, the services, realizing the importance of experimentation and indoctrination of flight personnel, acquired a number of low pressure chambers which were installed in the larger air stations. Originally, these chambers were used for experiment and research, but a certain amount of indoctrination was performed, and finally the authorities in charge of aviation training decided that it would be a wise procedure to utilize the chambers to indoctrinate aviation cadets or new flying personnel in the proper use of oxygen and oxygen equipment.

This was not only an excellent opportunity to teach how to use oxygen apparatus but also to show very clearly why oxygen was necessary. A standard indoctrinational run in the low pressure chamber was then developed, a phase of which was the elevation of each student to a simulated altitude of 18,000 feet, and his retention at that altitude until he could clearly demonstrate to himself the impairment that arose from oxygen want. Strange as it may seem, it was found difficult to develop a series of tests which would clearly show to the student that he *was* influenced by the lack of oxygen.

In the mass testing of numbers of cadets in the confines of the chambers, it is impracticable if not almost impossible to administer a physical performance test, and so we have had recourse to various psychologic tests, of which some require special instruments and others require rather complicated scoring. Practical tests have been tried, such as the performance of simple problems of navigation, and we have found that the most satisfactory was a simple test requiring the crossing out of certain letters in jumbled alphabetical sequence. Very recently, however, Professor Selig Hecht of Columbia has made use of the well-known anoxic loss of the visual discrimination sense, and has developed a contrast test which will be self-recording and which will, it is thought, very clearly indicate the fact that the discrimination of contrast is very much altered as the result of lack of oxygen. These tests are somewhat similar to the Luckiesh-Moss contrast discrimination charts but their self-recording feature will, it is thought, make them easier to use and simpler to score and will give the student a more vivid picture of his actually poor performance.

After the students have been allowed to remain at 18,000 feet for a certain period without oxygen, they are supplied with oxygen masks and allowed to go up to an altitude of 28,000 feet with oxygen, and there again repeat the tests with which they have had some difficulty, without oxygen, at the lower altitude. Following this stay at 28,000 feet, the descent is made as rapidly as is consistent with the ability of the students to equalize the ear pressure. This is sometimes a difficult problem. It requires that the student learn how to equalize his ear pressure in order to prevent the very painful and sometimes serious picture of aero-otitis media.

During the entire run, an observer within the chamber has spent as much time as possible imparting to the cadets or student pilots the basic principles of aviation physiology and in trying to impress upon the students the necessity for the use of oxygen and for its proper use under all circumstances. Whether the oxygen system used be of the rebreather type, the constant flow, or the demand type, a properly fitting mask is an essential for an efficiently operating system; and not only is this impressed upon the students, but tests of masks are made on their faces and those that are faulty in fit are discarded in favor of the proper type for each facial contour.

There have not been many reactions in this indoctrination run. Occasionally, the evidence of anoxia is markedly shown by cyanosis. There are a few cases of convulsions or perhaps loss of consciousness. Occasionally, and fortunately only occasionally, the startling picture of circulatory collapse is observed. But on the whole, the number of reactions is small and does not exceed 8 per cent.

In a succeeding run, which is called a classification run, the procedure is a bit different. In this run, the student is taken to 35,000 feet and kept there for an interval, eventually raised to 40,000 feet and then brought back to actual sea level. It is during this particular run that the student becomes acquainted with the symptomatology of aeroembolism or bends. These bends, which are produced by lowered atmospheric pressure, occur either as joint pains or as a combination of substernal pain and respiratory difficulty known as the "chokes." Abdominal distention does occur as the result of the presence of intestinal gas, and the distention may make the subject so uncomfortable as to require that the run be terminated. That, however, is not bends. Bends as most commonly observed consist of excruciating pain in the joints, and the pain may be so great as to become incapacitating. The most serious manifestation of bends is substernal pain with respiratory difficulty. The onset of this is the signal for an immediate drop in altitude, because it is thought that this particular syndrome may be indicative of cardiac involvement and, therefore, caution is required when it appears.

Although this run has been called a classification run, its validity as a means of classifying an individual's ability to withstand low pressure is open to serious question. Modifications in the run have been made and are still being made in an effort to devise a single test which will give an index of

the individual's susceptibility to bends. This has not yet been accomplished. It seems reasonably certain, however, that the individual who fails two consecutive runs to high altitudes—that is, develops incapacitating bends—is not the sort of person who would make a desirable member of a crew on a bombing mission at 35,000 feet. A man may develop bends at any time as the result of some extraneous factor, such as a dietary indiscretion, loss of sleep, or a hangover. But the probabilities are that the man who fails two consecutive tests in the low pressure chamber will develop bends more frequently than the individual who passes one single test.

But even if this classification test does not classify, it still has a valuable function. In the neighborhood of 34,000 feet, it is necessary that a man breathe 100 per cent oxygen in order to assure himself against the development of anoxia. Above that altitude, even though he breathes 100 per cent oxygen, he will develop an anoxia because the 100 per cent oxygen supplied at the mouth is not sufficient to maintain his alveolar oxygen tension at a level which will produce arterial saturation. Above 34,000 feet, then, it may be expected that an individual will develop a slight degree of anoxia. If his mask is not a perfectly fitting mask, it is obvious that the anoxia will be more severe and in fact may be extreme. One purpose of the classification run, then, is a demonstration to the pilots that a proper fitting mask and 100 per cent oxygen will protect them even at extreme altitudes of 40,000 feet.

The problems of anoxia and incapacitating bends are not by any means the only problems with which the flight surgeon must deal. He is intimately concerned with the selection and maintenance of pilots, and therefore with all problems concerned with those two functions. Anoxia and bends have been discussed in order to bring a wider realization that the flight surgeon is a part of aviation. Even in this war pilots have died because of failure of operation of their oxygen apparatus. Not many missions have yet been terminated because of incapacitating bends, but it is not at all beyond the realm of probability that many such missions will soon take place. We feel that if the flight surgeon can do something constructive toward eliminating the danger of anoxia, and thereby allow our pilots to go to higher altitudes, or prevent accidental and needless loss of life, or if they can by some means prevent the failure of a mission due to incapacitation as the result of bends, they will have accomplished something definite toward the winning of the war.

INDUSTRIAL MEDICAL PROBLEMS IN WAR PRODUCTION *

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There is probably no field of medical endeavor which is less static than Industrial Medicine. This is true primarily for two reasons: first, Industrial Medicine reflects the uninterrupted progress of medicine as a whole and, secondly, within its strictly occupational phases it reflects a multitude of changes which are constantly occurring at a more or less accelerated pace. The extent to which the industrial physician is aware of these changes and the degree to which he adapts his thought and procedure to them determines the value of medicine to industry and to the nation's war effort. We shall review briefly some of the problems and the changing needs, concepts and practices which confront Industrial Medicine today.

The vast increase in industrial personnel is a matter of general knowledge. Many industrial organizations have grown to twice their prewar size. In numerous instances, in fact, increases in the number of employes have reached to 500 per cent or more of the figures of two years ago. This growth should, normally, have been accompanied by a commensurate growth in plant medical departments. Such, however, has not been the case. Physicians have not been generally available to fill the demands of industry, and training facilities for those available have not generally been adequate to introduce the practitioner to the specific duties of industrial medicine. To a considerable degree, these problems exist with respect to industrial nurses. It is, therefore, obvious that we are, at present, faced with a heavy multiplication of duties and at the same time we are confronted with a more or less serious curtailment of professional personnel as well as physical layouts.

However, the pressing questions of the moment are not simply quantitative ones. There are weighty questions which involve qualitative changes. We no longer find ourselves in our accustomed setting with respect to our industrial personnel. The character of the working group has changed and, in many instances, the change has been drastic as well as abrupt. The free selection of the physically strong and unhandicapped is no longer our privilege. We are making compromises that none had anticipated when the physical requirements for employment were defined some years past. An interesting and often repeated observation is that many of our standards were arbitrary and not necessarily accurate so far as job efficiency is concerned. The social, humanitarian, and medical implications of this revelation are too great to allow treatment in the brief space allotted us. It is, however, certain that the invasion of industry by the older worker, the handicapped, and

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the woman employe will force a revision of previous concepts of job fitness. We are placed, for the first time in industrial history, in the position to determine what the potentialities of these new workers actually are. We shall learn much from our current experience and, if we learn our lesson well, the future contribution of industrial medicine to human welfare will exceed the highest hopes of our most sanguine colleagues. We shall henceforth easily prove the industrial usefulness of the uncounted thousands who, measured by conventional criteria, were declared unemployable and relegated to a state of helpless dependency and spiritual and moral stagnation. Even at this moment, we can readily prove the feasibility of salvaging a staggering proportion of our older workers and of our handicapped for useful and productive lives. Witness the skilled mechanic, several years retired, who resumes once more the competent performance of his work. Witness, also, the successful employment of the orthopedic case, the cardiac patient, the visually handicapped, the hard of hearing, and still others whose mention space will not allow. To be sure, careful and painstaking job placement and follow-up have been required but the effort has been well worth while.

The employment of women workers has revealed their astonishing competency in a variety of occupations formerly held to be the exclusive prerogative of men. At Westinghouse we have 25,000 of them. We have selected them on the basis of the same physical standards now applied to men. To be sure we have had the usual experience with respect to absenteeism, but there is ground for the belief that domestic and social problems may well outweigh the medical ones in the greater absenteeism of the women workers.

The constant need of measures for the control of industrial hazards is more acute than ever. New materials and processes are being introduced at a rapid rate. The present restricted use of toluol has, for example, led to the introduction of solvents containing a considerable amount of benzol. The latter not only has a much lower maximum permissible concentration, but has a much higher rate of evaporation so that a toxic air concentration is reached much more readily with benzol than with the toluol it supplants. This has led to careful efforts at control including determinations of vapor concentrations, periodic examinations, urine sulfate determinations, the enclosing of processes, improving ventilation and providing adequate exhaust installations.

Restrictions on the use of tin required, in the case of a non-ferrous alloy, a change in formulation with added amounts of lead and the use of a small proportion of arsenic. Determinations of air concentrations were made to check on the possible presence of hazards which, in this instance, were not found to exist. However, the change described necessitated the tests to prove the absence of a health hazard. Such problems constantly are arising.

It is evident that Industrial Medicine is vitally concerned with the conservation of manpower not only because of the critical needs of the time but also because this is an ever present objective. It should, perhaps, be empha-

sized that the employment of the handicapped in itself opens a large and hitherto untapped reservoir of manpower. There are, however, other means of saving manpower and we shall refer to a few of the effective current measures.

The traditional first aid practices must be given their due share of credit for decreasing lost time. Although they are, by no means, the sole interest of medicine in industry, they are, nevertheless, vital. Prompt attention to minor accidents prevents the major disasters of complications. Early detection of illness often shortens periods of disability. Even the symptomatic treatment of transient ills, if intelligently carried out, lowers the loss of working time. It would seem legitimate to view this function of Industrial Medicine as an indispensable phase of its work; it should not, of course, be the sum total of its activities.

The modern program of physical examinations is a large factor in conserving manpower. It avoids waste first of all by the careful placement of applicants. The loss in efficiency and the turnover due to the one factor of misplacement have always been of great magnitude. The effort to insure, at the outset of employment, that the job and the worker are compatible physically and psychologically will reduce this great loss. After the worker has been correctly placed, the periodic examination, performed at intervals determined by the hazards of his work, will help immeasurably to safeguard his physical welfare and will avoid loss of time due either to the external hazards of the job or to the internal dangers of incipient ill health. The transfer examination will insure that change of job in the course of employment will not result in the misplacement which the preplacement examination sought to avoid. The special examination, performed at any time dictated by illness or special need, adds to the manpower savings effected by the other examinations mentioned.

As already intimated, laboratory studies are used as adjuncts to the physical examination. Lead, mercury, and sulfate urinary determinations, as well as a variety of other tests, supplement both the physical examination and the measures taken to control the shop environment and remove from it any substance or condition which is a threat to health.

An industrial health problem which has been too often neglected in the past is the physical welfare of the supervisory group. Only the tremendous stress of war has served as an effective reminder that the industrial executive is human material subject to the ills and the hazards that generally threaten the health of workers. There are certain factors which constitute a particular danger to the executive. His hours of work are, first of all, undefined. Conventional practice plants him at his desk for the eight hours of the working day. Today, in many instances, these hours have been greatly augmented. However, his work is measured not by time served but by goals achieved and by the successful execution of duties often remote from routine and repeated functions. It is inevitable, therefore, that his working

day extends far beyond his recognized hours of employment. He is with his work wherever he may be, and its perplexities, vexations, and its uncertainties are companions at his table and intruders in his bed. The tension of the job becomes the tension of much of the entire day with its accompanying physical and mental manifestations. Many companies are now recognizing these facts and taking the necessary remedial steps. At Westinghouse, we have, in the past several years, made a definite effort to safeguard the health of our supervisors through the provision of complete physical examinations and the reference of the findings to the executive's own physician for whatever therapy might be indicated. In the past year we made a fairly complete cardiovascular study of 909 supervisory employes ranging in age from 25 to 74 years. Many abnormalities were, of course, found. Their incidence increased greatly as the 40 year old group was reached and rose rapidly above this age. Hypertension, for example, increased markedly with age. It did show a decrease in the oldest cases simply because hypertensives are not apt to survive to reach the more advanced ages included in our surveys. Cardiac abnormalities were found in 23 cases who had never offered any complaints relative to the heart. In 53 cases giving a history of cardiac complaints, heart disease was found in 42. The great need of health programs for the executive should be apparent without further comment, particularly at a time when so much depends on his well-being and efficiency.

The war has given unprecedented impetus to nutrition programs in industry. Proper nutrition has long been recognized as basic to health. Knowledge of the nutritional essentials is, undoubtedly, of very great importance in maintaining the health of the industrial worker, in safeguarding his efficiency on the job, and in contributing to the reduction of absenteeism.

Health education was adopted by progressive industrial medical departments in industry many years ago. Several large companies have highly developed educational programs as part of the health service offered their employes. The value of this work is sufficiently well recognized to induce certain companies to maintain highly trained staffs and to expend large sums of money for the promotion of health education. Usually, the educational medium is literature issued to the workers. Other means such as lectures, demonstrations, visual materials in the form of slides, films, posters, displays, and so forth are also in use although to a lesser extent than their value as educational devices might justify. At Westinghouse, we have, in the past year, issued health leaflets, booklets, and posters dealing with such subjects as the common cold, obesity, tuberculosis, nutrition, posture, care of the feet, dental care, etc. The most extensive phase of last year's program has consisted of a series of eight leaflets constituting a fairly extensive course for the layman on the character of tuberculosis and the means of prevention. We considered it necessary to stress this subject because of the increased threat of tuberculosis in war time and because of the fact that we have noticed an increased incidence in the past several years among our own

workers. This increase is, however, probably only apparent and may be due to an enlarged periodic examination program.

Absenteeism is a problem which has been greatly accentuated by war. When each working hour is an added assurance that the material implements of war will be available, each lost hour is a threat to national security. Extensive absenteeism can well become a danger of disconcerting magnitude. The problem is far too complex to permit more than passing mention here. There are certain aspects which we may at least point out as deserving of special study. First of all, we wish to express the point of view that efforts at the reduction of lost time from whatever cause must be unremitting. Purely hypothetical treatment of the problem is ineffective; definite and reliable data capable of analysis and interpretation are necessary. Since the incidence of absence seems to concentrate in a certain group, in fact, in a relatively small minority of workers, efforts at prevention must deal primarily with this group. Moreover, it is utterly fruitless to attribute the vast majority of absences to incapacitating illness. This explanation is one easily rendered but not as yet based on adequate proof. Domestic problems, socio-economic problems, personality problems may well take precedence over the purely medical ones. For several months we have gathered data on absenteeism at Westinghouse. In our plants for the month of March 1943 the normal working hours were 11, 112, 563. Voluntary absence accounted for 1.91 per cent of this time; illness for 2.58 per cent; vacations for .55 per cent; furloughs for .52 per cent; and other causes for .18 per cent. Excluding vacations, there was a total of 5.19 per cent. The total lost hours amounted to 576,742.

Such facts must suggest caution in the analysis of these data. Furthermore, for a variety of reasons, data on illness are frequently open to question. From the standpoint of health and accident prevention, we are exerting every effort to curtail this loss. Our medical program is keyed to this objective. Other agencies associated with us are attempting to reduce absenteeism to the lowest possible minimum. Continual further study and persistent efforts to seek the basic difficulties and to remedy them are only measures which will mitigate the evils of this problem.

It is clearly evident that Industrial Medicine faces many weighty responsibilities. To its ordinary burdens are now added the critical problems of war. We are confident that in this moment of great national need we shall meet these problems effectively and that we shall safeguard the physical welfare of our workers with greater vigilance than ever before. We shall thus insure the high productive capacity which industry must maintain to bring the war to an early and victorious termination.

THE MANAGEMENT AND PREVENTION OF CIVILIAN WAR GAS INJURY*

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THE various kinds of war gases, their methods of action, and routine clinical procedures for handling injuries from them have been abundantly publicized in various monographs, brochures, and "official" pamphlets. The uniformity of organization of these tracts suggests that many of them are simply slight modifications of similar publications issued 25 years ago. Fortunately, during the past year, under the auspices of the civilian preparedness organizations, some revision has occurred which is based on increased knowledge and wiser application of it. More attention is being paid to the mechanism of action of war gases, and there is broader understanding of psychological factors involved in their use.

War gases are both military tools and political and psychological weapons. General public ignorance of war gases tends to produce fear of them. This fear in turn may engender panic on the threat of their possible use. The tendency towards this undesirable panic may be prevented by dispelling the ignorance through furnishing as much information as possible regarding war gases and thus reducing public fear of them. If people can be taught the relatively simple means by which civilians may be protected against war gases, there would certainly be less tendency for panic, should war gases actually be thrown against us.

Total war is a relatively new experience for most of us, and we are by no means prepared for it. Civilian effectiveness in total war depends on our ability to carry on in the face of whatever may happen. We have a splendid example of this in England. It is important for civilians to differentiate between the conditions under which soldiers must carry on and those which are possible for civilians.

The function of a soldier is to seize, occupy and hold ground. To hold land exposed to war gas, soldiers must be carefully and fully protected. Civilians, however, may take shelter and may go away from places which are likely to be bombarded or exposed to war gases. Civilians do not need the elaborate protection against war gases which is necessary for soldiers. These considerations have significant economic and political consequences in connection with the possibility of panic from the use of war gas.

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Economic Aspects of War Gas Action

Most importantly civilians should appreciate that it is possible to improvise reasonably satisfactory protection against whatever war gas may be thrown at them, without the need of gas masks or protective clothing. Gas masks take steel and rubber. Protective clothing for civilians requires material better used for military purposes. If we were to provide masks for all civilians who might be exposed to war gases, an enormous tonnage of steel and rubber would be diverted from offensive weapons. Fortunately the demand for gas masks for civilians is diminishing. Our enemies watch these demands closely. The demand for gas masks for civilians is an index of civilian panic potential. If the demand is great, it is an indication that the people in general are ignorant of war gases, and it may, therefore, be reasonably assumed that they are afraid of them, and that panic is likely to ensue if war gas is used against them. If our enemies can make us afraid of war gases and if they can persuade us that we must have gas masks with which to protect ourselves, they know that they will not suffer as severe offensive action as if we were to turn every bit of our steel and rubber against them. Let us remember that the best way to protect ourselves is to beat our enemy in his own back yard. That we are now so doing is perhaps one reason why our panic potential with respect to war gas is falling. Let us remember, however, that another war may come and that we should be getting ready for it now.

Psychological Action of War Gas

In May 1942, Prime Minister Churchill and President Roosevelt solemnly joined in warning our enemies against the use of war gases. They stated that if war gases were used against us or our allies, we would promptly retaliate. They both went on to imply that the use of war gas is uncivilized, indecent, and inhumane. It is quite obvious from their statements, however, that we are fully prepared to use war gas if necessary. Obviously the statement that war gases are indecent and inhumane and that no civilized country would use them was designed for its psychological effect. It is desirable to promote a feeling of guilt in one's enemies. It is desirable also to issue solemn warnings about what may happen in case the enemy does something that one may not wish him to do. But it is necessary to win. So far we have always won, and then it becomes very convenient at the peace table to fasten guilt upon our erstwhile enemy. It is necessary that we understand these matters in order that we shall not be fooled by the psychological trap we are attempting to set for our enemies.

It is interesting that these factors were first emphasized by Curt Wachtel,[1] who had served under the celebrated Fritz Haber at the Kaiser Wilhelm Institute of Berlin during World War I. Our enemies know precisely what these various factors are, and they were able to use them with profound effect

against us. The threat of the use of war gases against the English, following Munich, resulted in the provision of gas masks for everyone in Britain, but prevented the manufacture of enough airplanes to keep off the Luftwaffe during the horrible 1940 bombings.

It is remarkable that war gases have not yet been used to any great extent in this war. They are reported to have been experimented with both by the Germans and the Japanese. However, this is a war of rapid movement. No military commander wishes to be *bothered* with war gas if it is possible to avoid its use. War gas interferes with the efficiency of troops to the extent of at least 80 per cent. As soon as the situation becomes desperate, war gas may be used. However, our air superiority may make the Germans and Japs genuinely afraid to use war gas through fear of retaliation. The psychological value of our warnings may thus be justified, *as long as we retain the power.*

War gases are effective and relatively humane weapons. The gross over-all figures for World War I show that 2 per cent of those injured by exposure to war gases died as a result of the exposure. On the other hand, the mortality among those injured from exposure only to shot, shell, and bayonet was 24 per cent. It is much easier to devise intelligent protection against war gases than against shell and bayonet. The after-effects of exposure to war gas are not so serious as commonly supposed. A survey by the United States Public Health Service showed that there was no greater incidence of lung disease, circulatory disorder, or other physical disability in those exposed to war gases than in the same comparable age group of the general population.[2]

Of course, new war gases may be used. Many are possible, and certainly mixtures will be employed. *It is ridiculous to recommend protection to civilians on the basis of specific identification of any single war gas.* This takes time, is uncertain if attempted by smell alone, and is unsound psychologically, since doubt might arise that the agent had been correctly identified. It is much wiser to *devise methods of protection for civilians against war gases that will take care of anything that may be suspected.*

It is very important to give civilians as much information about war gases as possible. It is wise to give information of how they act biologically, and how their action may be prevented or reduced. If this is carefully done, it will become readily apparent that one may reasonably take care of oneself no matter what kind of war gas may be suspected.

It is extremely important to point out that all explosions release "war gases." In addition to carbon monoxide, which is odorless, colorless, and nonirritating but which fortunately dissipates very rapidly, there are also "nitrous fumes," and the effects of "blast." The action of any of these accompaniments of explosions may be confused with the action of war gas. "Nitrous fumes" are brownish, heavy vapors which will irritate the eyes and nose and lungs, and cause effects very similar to the war gases. The methods

of protection devised for war gases are equally effective against "nitrous fumes," or even against hot oil smoke or the smoke and fumes from other incendiaries. Reasonable appreciation of the biological action of war gases will tend to remove the untoward psychological effects of fear of exposure to them.

Biological Action of War Gases

The intensity of biological action of a chemical agent is dependent upon: (*a*) *dosage,* in terms of mass of chemical per mass of living material; (*b*) *ratio* of the *rate of absorption* and distribution of the drug through the living tissue to its *rate of excretion* or destruction; (*c*) *physicochemical properties* of the drug, such as its differential solubility in different solvents, its polarity, its molecular configuration and energy organization, its dissociation characteristics, and its optical properties; and (*d*) *peculiarities of the particular type of living tissue involved,* such as its age, its metabolic and allergic states, and its enzyme balance.

Appreciation of these factors may help to understand the difference in action of various war gases and the variation in intensity of effect of the same war gas in the same concentration on different individuals. A suitable analogy to the latter situation is the difference in response of different people to the same intensity of sunlight or poison ivy.

For our present purposes we may consider as ordinary war gases the lung irritants, like phosgene or chloropicrin, or the vesicants, like mustard gas and lewisite. We may thus disregard such unusual possibilities as catalyzed cyanides or metallic carbonyls, and such gaseous associates of

Table I

Chemical Relations Between Common Irritant Drugs and War Gases

Aliphatic Irritant	Corresponding War Gas
Alcohol $H—CH_2CH_2—OH$	Ethyl dichloroarsine $H—CH_2CH_2—AsCl_2$
Chloroform $Cl_3C—H$	Chloropicrin $Cl_3C—NO_2$
Ether $(H—CH_2CH_2)_2O$	Mustard Gas $(Cl—CH_2CH_2)_2S$

demolition bombs and incendiaries as carbon monoxide, "nitrous fumes," "blasts," hot oil smoke, or phosphorus. However, the tissue aggressiveness of "nitrous fumes" suggests that these deserve attention in the same way as ordinary war gases.[3] The hush-hush "nitrogen mustards," which the Germans may use, are obviously alkyl amine relatives of ordinary mustard gas, but have the advantage of little odor and of "nonfreeze." They are "ordinary" war gases.

As shown in table 1, the ordinary war gases may be indicated to be chemically related to such types of aliphatic hypnotic and inhalation anesthetic agents as alcohol, chloroform, and ether. People generally recognize

the locally irritating powers of these common compounds. Their gas relatives may owe an increased irritative action to aggressive factors associated with altered halogenation and polarity.

These war gases usually contain a rather labile halogen, like chlorine or bromine, which, with the hydrocarbon portion, may be considered to be relatively more attracted to fat and protein than the rest of the molecule. On the other hand, the war gases also contain more potent polarizing radicals, like oxygen, sulfur, arsenic, a nitro group or oxime, which may be relatively more attracted to water or which may reduce the strength of the halogen bond. Differences in relative water-fat solubilities and in ease of hydrolysis may be important factors in the site of action or in the onset or duration of action, as exemplified in the contrast between lacrimators and vesicants.

A common theory explains the action of war gases on the basis of splitting off of halogen, with immediate irritant effect from the resulting halo-acid. This may occur promptly on the wet surfaces of eyes, and of mucous membranes of the nose, mouth, and lungs, with such agents as the lacrimators, phosgene, and lewisite. On the other hand, as with mustard gas, the partition coefficient may favor absorption into the cells, after which the halogen may split off. The resulting halo-acid within the cell may alter enzyme systems, permeability of the surface membrane or protein equilibria, in such a way as to kill the cell. Although such formation of acid may occur, it would have to exceed the buffering capacity of cells and tissues, and this might require relatively large amounts in order to pass the threshold. Neutralization by cellular buffers would be expected to produce the corresponding halide ion which would not markedly affect cellular function. At any rate, exhaustion of the buffer mechanism should reduce further hydrolysis. Direct experiment has shown that molecularly intact mustard gas may be isolated from deep skin layers many hours after absorption. Again, acid injury usually involves protein denaturation and precipitation, whereas war gas injury is characterized more by disturbances of cellular permeability, with swelling, protein hydrolysis, and cellular disintegration.[4]

Another theory of mechanism of action may be considered. This relates to the relatively rigid molecular configuration of the war gas molecule as compared to the cell membrane. The latter is interpreted as a water-lipo-protein interface.[4] Portions of the war gas molecule seem to be relatively lipo-proteophilic, whereas other portions seem to be more hydrophilic. If enough war gas molecules are present at the cell surface, distortion of the interface may occur. This would result from orientation of the war gas molecule in accordance with the selective affinity of different parts of the molecule for water and lipo-protein, respectively. If this affinity and the interatomic angle forces in the war gas molecules are greater than the surface tension forces which maintain the normal cell surface, torsion may follow, with changes in permeability of the surface film, and resulting swelling and further distortion and strain of the surface membrane. This may com-

prise the initial inflammatory response to war gases, which may go on to cellular rupture, release of histamine, vascular breakdown, autolysis, and necrosis, as so well described by Livingston and Walker.[5] Tight packing of cells, as may be accomplished by high ascorbic acid intake,[6] would tend to reduce the intensity of this reaction as Livingston and Walker noted.[5]

Also involved may be allergic reactions to protein combinations with war gases or their decomposition products. Allergic reactions may depend in part on disturbances of cellular permeability with resulting swelling and distortion of cell surfaces which may go to the point of rupture and subsequent necrosis. In general those individuals with sensitive skins and mucous membranes are much more apt to be severely injured by contact with war gas vapor or the liquids, than are persons with tough, dark skins. Negroes are particularly resistant to skin effects of war gases.

Whichever mechanism occurs, the prolonged tissue response to war gases would subsequently include the slow removal of necrotic debris, to be followed by gradual repair. In the case of lung irritants, this sluggish process indicates the need for protracted oxygen administration as well as for prophylaxis against psychogenic pneumophobia. Skin injury from war gases is similar to that produced by a burn, and the same type of treatment is indicated as in the case of burns. Blisters should be drained carefully. There is conflicting evidence regarding the toxicity of blister fluid, but in general the evidence indicates that these fluids are not so dangerous as was at first suspected. Subsequent treatment of skin injury should be in accordance with the physician's favorite method of handling burns, which in general means (1) providing a protective covering, or eschar, by means of medicated warm wax, tanning, or by the use of antiseptic dyes; (2) preventing infection, and (3) restoring body fluids. In the case of suspected injury to the lung, oxygen administration is necessary for at least two weeks or more to include the total repair period. If oxygen administration is stopped before the removal of the necrotic debris, there may be sudden collapse of the patient with fatal consequences.

Skin injuries from war gases require careful management. Itching is often intense. Scratching is difficult to control, and often skin is removed with subsequent infection. The British use amyl salicylate to control itching from mustard gas exposure. Benzyl benzoate might be expected to be equally as effective. Denuded areas are very tender. Local anesthetics should be used with caution, since local application may result in the formation of para-aminobenzoic acid from ordinary local anesthetics, which may promote bacterial metabolism and antagonize sulfonamides, if the latter are used to control infection. Local anesthetics not likely to yield para-aminobenzoic acid may be dangerous as a result of absorption. Benzoyl peroxide or urea peroxide might be included with sulfonamides in preparations for local application. These peroxides are mild local anesthetics as well as mild oxidizing antiseptics. They may also help to promote healing.

Large areas which may be vapor burned (reddened with tiny or no vesicles after 24 hours) require little treatment, except control of itching. If scratching is controlled and if the minor vesicles are not opened, healing may be complete within 10 days. Mild vapor burns may appear on parts of the body covered by clothing, as a result of unnoticed gas droplets on the clothing, with resulting slow diffusion of the gas through the cloth.

Vesicles smaller than six millimeters in diameter should not be drained, as the skin will often retain sufficient vitality to act as a protective covering for the area and thus keep out infection. Pressure blisters on the edges of palmar surfaces or under calloused areas will usually be reabsorbed if left alone. These blister areas may turn brown, but there is usually no scarring.

Vapor burns in the axilla and perineum are distressing. Hot weather aggravates reactions in these areas. Following vapor irritation, continued sweating adds to the discomfort during repair and recovery. Saline packs and saline baths may afford some relief. Mild oxidizing solutions, such as a weak, buffered hypochlorite solution, or Dakin's solution, may be soothing.

The hands are readily contaminated with vesicant gases. The tender, often sweaty areas between the fingers are attacked rapidly. Vesicles forming on these surfaces may be painful and may rupture. Calomine lotion has been used, but healing is slow.

Large skin areas denuded by vesicant gases produce an exudate more extensively than in the case of an ordinary burn. Tannic acid or silver nitrate eschars are not always satisfactory, perhaps because of the devitalized condition of the tissue beneath as well as the pressure exerted by the exudate. Perhaps the medicated hot wax spray, such as recommended by Pendleton,[7] would be more suitable. If the eschar loosens or comes off, the attempt to produce a new eschar may be unwise. The incidence of infection rises rapidly. Whereas heat burns are usually sudden affairs, with acute damage, chemical burns from vesicant gases are more chronic and prolonged in their course, and the continuing action of the chemical remaining in the tissue may make treatment difficult.

In the biological effects of war gases, therefore, it seems that one or more of the following factors are concerned: (*a*) relative water, fat, and protein solubility, both in transport and in relation to cell surface; (*b*) relative ease of hydrolysis, with relation to possible formation of halogen acid and the effects of the rest of the molecule; (*c*) distortion of cellular surfaces due to the molecular configuration of war gas molecules or to their secondary valence forces; (*d*) effects of war gas molecules on pH, redox potential and colloid, interface and enzyme equilibria; and (*e*) allergic factors as a result of possible tissue reactions to combinations between protein and war gas decomposition products.

As in the case of sunburn or exposure to poison ivy, once the process of war gas injury is under way, one may hope for benefit only on the basis of symptomatic relief, of aiding the removal of necrotic tissue, and of pro-

moting repair. It would seem wise, therefore, to train civilians in "self aid" against war gases in suspected contact with war gas, since first-aid or professional care is apt to be too late.

Self-Aid Against War Gases

In order to reduce confusion of thought to a minimum and thus to help prevent panic in suspected attack with war gas, "self-aid" should be devised in as simple a manner as possible. Recommendations should be based on the effectiveness for whatever is likely to be used by a clever enemy. Since mixtures of war gases are certain to be employed, it seems unwise to worry about specific identification and specific management of potential injury, if such identification is based on such an indefinite procedure as smell.

Absorption of the ordinary war gases and their many obvious chemical relatives, such as the "nitrogen mustards," may be inhibited by neutralizing hydrolysis, oxidation, or adsorption. For civilian use, these methods may be improvised from materials readily available in homes. Since the war gases, in general, are decomposed or poorly soluble in water, a wet cloth tied over the nose and mouth is a relatively effective barrier for a short while at least, to the passage of such vapors, including oil smoke and "nitrous fumes," to the nose, throat, and lungs.

The most readily available effective oxidants are the common kitchen bleach solutions, such as "Clorox." These are buffered, 3 to 5 per cent sodium hypochlorite solutions and are nonirritating for blotting the skin, but should be diluted for application to mucous membranes, for washing the skin or for wetting cloths to breathe through. As is well known, such a solution reacts promptly with mustard gas, 2, 2-dichlorodiethyl sulfide (b.p. 217° C.), converting it to the water soluble nontoxic crystalline 2, 2-dichlorodiethyl sulfoxide (m.p. 110° C.) and probably to other nontoxic sulfones. The use of such sodium hypochlorite solutions for the prevention of mustard gas injury has been widely advertised in England.[8] Confirmation of their effectiveness against both mustard gas and lewisite has been obtained by T. D. Stewart, of the University of California, Berkeley, on scores of human subjects, and by ourselves on human cases and experimental animals. It is immaterial whether oxidation of mustard gas produces the sulfoxide or sulfone, or further decomposition, or what is produced on treating lewisite with hypochlorite. Direct experiment shows that such treatment of these compounds or their various chemical relatives results in residues which may readily be flushed off the skin with soap and water.

For alkaline hydrolysis, sodium bicarbonate solutions of about 2 per cent may be readily prepared in a blackout room by dissolving a teaspoonful of baking soda in a glass of water. Such a solution is helpful in washing out the eyes, nose, and throat in suspected war gas irritation, or for wetting cloths to breathe through.

The most suitable and readily available detergent adsorbent is lather from ordinary soap and water, or soap flakes, or tincture of green soap. This is particularly useful, as are hypochlorite solutions, in preventing skin injuries from suspected contact with blister gases. Soap and water is highly effective for removing vesicants such as mustard gas and lewisite from intact skin if used from three to eight minutes after exposure. If the delay is longer than this, the vesicant penetrates deeply into the skin surface lipoid material, particularly concentrated around hairs, where it is not easily removed by soap and water or mild oxidizing agents.

Various detergents have been investigated in order to determine whether they are more effective than soap and water. Aliphatic monoamines with 12 to 18 carbon atoms will preferentially absorb mustard gas or lewisite in comparison with skin lipoids, but the complete removal of the amine from the skin is difficult, and any remaining material may cause damage. Sodium alkylsulfonates and sodium dialkylsulfosuccinates are equal in activity to soap, although their emulsions of mustard gas and water are unstable. The alkaline detergents and the partial fatty acid esters of sorbitan are unsatisfactory for they are poorly water soluble. The acid acitergeols and the polyoxyalkylene derivatives of sorbitan monolaurate are most effective in removing mustard gas dissolved in lipoid or high molecular weight amines. However, they must be used within 10 minutes after liquid mustard gas contamination if they are to prevent skin injury. It seems, therefore, that immediate use of soap and water is the most readily available effective detergent for preventing war gas blistering.

The data in table 2 show the value of soap and hypochlorite in reducing skin injury (in a rather sensitive test object) from mustard gas application, in comparison with such a mustard gas solvent as kerosene. The common blister gases are soluble in kerosene, gasoline, acetone, carbon tetrachloride, and similar fat solvents. During World War I, it was naturally assumed that such solvents would be useful in removing liquid blister gas splashed on the skin. We have found no data to support this idea. However, advice to civilians may still retain this recommendation. It is to be remembered that kerosene, gasoline, and acetone may be absorbed through the skin, and that, like carbon tetrachloride, they are themselves skin irritants. They are also solvents of low viscosity and tend to spread easily. It is unlikely that they would be used carefully under the conditions of excitement existing in the crisis of suspected war gas contact. Our experiments show (table 2) that even under controlled conditions they are much less satisfactory than lather or hypochlorite.[9]

A study was made of characteristic "nitrogen mustards." 2-Chloroethylamine, bis-(2-chloroethyl)amine, tris-(2-chloroethyl)amine, 2-chloroethyl-dimethylamine, and bis-(2-chloroethyl)methylamine are liquids to low melting solids with faint odor and high volatility. They produce blisters more rapidly than mustard gas, although the blisters are slightly less severe.

TABLE II

Comparative Skin Response in Rabbits to Mustard Gas (HS)

Application of 0.05 c.c. of 10 per cent solution of HS in ether, producing rough circle 10 mm. in diameter. Treatment consisting of blotting area of application three times with gauze soaked in kerosene, soap and water, or 3 per cent NaOCl (Clorox).*

Day	Untreated	Kerosene	Soap	3 Per Cent NaOCl
1	Intense erythema and edema	Moderate erythema, slight edema	Diffuse erythema, edema	Diffuse erythema
2	Diffuse erythema and edema, central blanched area	Diffuse erythema and edema, central blanched area	Blanched area, 10 × 15 mm.	Blanched area, 10 × 15 mm.
5	Deep hemorrhagic necrotic area, 10 × 12 mm.	Hemorrhagic necrotic area, 12 × 15 mm., with diffuse necrosis at edges	Thin scaly necrosis, 8 × 10 mm.	Thin scaly necrosis, 8 × 10 mm.
15	Heavy adherent scab, 10 × 12 mm.	Broad, adherent scab, 15 × 20 mm.	Thin flaky scab, 8 × 10 mm.	Thin flaky scab, 8 × 10 mm.
22	Heavy adherent scab, 10 × 12 mm.	Broad adherent scab, 15 × 20 mm.	Light scar	Light scar

* No significant difference from untreated areas observed after application (as above) of either 3 per cent H_2O_2, acetone, or "bleach paste." Treatment with 5 per cent NaOH in 30 per cent glycerin seems to increase inflammatory reaction during the first week, producing a deeper and slower healing necrotic area. Ten per cent benzoyl peroxide in nona ethylene glycol seems to have little effect on HS reaction during first day or so, but seems to reduce necrotic reaction and time required for healing. However, 10 per cent benzoyl peroxide in talc affords no protection when dusted on skin previous to exposure. Observations similar to the above have been obtained with lewisite; healing, however, is more rapid.

Rubber is more rapidly penetrated by these compounds than by mustard gas. It is likely that these haloalkylamines may be used tactically as single compounds, mixtures, or mixtures with other vesicants such as lewisite or mustard gas.

Although the "nitrogen mustards" are soluble in acids, the acid salts are also vesicants. In general, basic substances intensify their action before destroying them by hydrolysis, unless the basic material is so vigorous that it also destroys intact skin. The common oxidizing agents are somewhat more satisfactory for preventing skin injury from the "nitrogen mustards." Organic solvents will spread "nitrogen mustards" on the skin in the same way as they will spread mustard gas or lewisite, lessening the intensity somewhat, but producing wider action. Various detergents will remove the "nitrogen mustards" completely from the skin if used within five minutes after contact. Although acid detergents are most efficient in removing "nitrogen mustards," basic detergents are best for the other vesicants. An abundance of soap and water seems to be effective for all the vesicants, and more readily available to the average civilian than any other protective material.

Civilian Protection Against War Gases

Pharmacologists have the obligation of establishing and explaining the facts regarding the action of chemicals on living things. They have the privilege of applying such information to whatever practical problems may be appropriate. With respect to war gases, present pharmacological information suggests that the simplest and most effective advice for civilian protection against such gases might be: (*a*) obey air-raid rules, taking refuge during an alarm in an air-raid shelter or blackout room, with doors and windows shut and the windows screened or heavily curtained on the inside to prevent injury from flying glass, if bombing occurs; (*b*) if the shelter is broken by bombing, and if war gases are suspected by fogs, peculiar odors, smarting or stinging in the eyes, nose or throat, or by coughing, sneezing or gasping, or by any other suspicions, tie a cloth soaked in baking soda solution, or diluted kitchen bleach solution, over the nose and mouth to breathe through, keep it wet, shut one eye and squint through the other, lie down with head in arms; (*c*) if eyes, nose or throat are irritated, wash them with a solution of a teaspoonful of baking soda in a glass of water; (*d*) if splashes of liquid are suspected on the skin or clothes, throw the outer clothing out the window, blot any splash on the skin promptly and repeatedly with a cloth wet with kitchen bleach solution, lather thoroughly and frequently with soap and rinse copiously with water. If subsequent injury results, the management is symptomatic at a casualty station or hospital.

These considerations were fully reviewed early in 1942 by the San Francisco and Alameda Committee on the Medical Aspects of War Gases.[10] Special discussions along these lines have been widely published on the West Coast for civilian information.[11] Experience has shown that these sug-

Table III

Comparison of Methods of Treatment in Dogs for Exposure to Mustard Gas

Applied in 5 mg. droplet to the skin. Treatment after 5 minutes, with swab

Day	Untreated	Bleach Paste	5 Per Cent NaOH in 30 Per Cent Glycerin	Kerosene	Soap	3 Per Cent NaOCl
1	Intense erythema and edema	Intense erythema and edema	Intense erythema and edema	Moderate erythema, slight edema	Diffuse erythema, slight edema	Diffuse erythema
2	Diffuse erythema and edema, central blanched area	Diffuse erythema and edema, central blanched area	Intense erythema and edema, central blanched area	Diffuse erythema and edema, central blanched area	Blanched area, 25 × 30 mm.	Blanched area, 25 × 30 mm.
7	Deep hemorrhagic necrotic area, 25 × 30 mm.	Deep hemorrhagic necrotic area, 25 × 30 mm.	Deep hemorrhagic necrotic area, 25 × 30 mm.	Hemorrhagic necrotic area, 30 × 45 mm.	Thin scaly necrosis, 20 × 25 mm.	Thin scaly necrosis, 20 × 25 mm.
14	Heavy adherent scab, 25 × 30 mm.	Heavy adherent scab, 25 × 30 mm.	Heavy adherent scab, 30 × 40 mm.	Broad adherent scab, 35 × 45 mm.	Thin flaky scab, 20 × 25 mm.	Thin flaky scab 20 × 25 mm.
28	Heavy adherent scab, 25 × 30 mm.	Heavy adherent scab, 25 × 30 mm.	Heavy adherent scab, 25 × 30 mm.	Broad adherent scab, 30 × 35 mm.	Light scar	Light brown spot

TABLE IV

Comparison of Methods of Treatment for Exposure to Mustard Gas

Treatment 5 minutes after application of 5 mg. HS to dog belly

Acetone Alcohol Gasoline	Similar to kerosene. Questionable value
3% H_2O_2 2% $NaHCO_3$	Similar to untreated unless affected area is continuously immersed in solution. Questionable value
Aerosol OT Aerosol MA Aciterge-OL Alkaterge-O Span-20 Span-60 Span-80 Tween-20	Similar to soap and water. Some better than others. Unavailable to general public during wartime
Urea peroxide Ammonium persulfate Sodium percarbonate Sodium pyrophosphate-peroxide	Similar to strong sodium hypochlorite solutions. Must be used with care. Unavailable to general public during wartime
Magnesium peroxide Zinc peroxide	Ineffective
Chloramine-T Dichloramine-T Chloramine-B Dichloramine-B Halozone	Various formulations similar in action to 3 per cent sodium hypochlorite. Unavailable to general public during wartime

We are grateful to the Atlas Powder Company, Wilmington, Delaware, for generous samples of Atlas Spans and Tweens; to the Commerical Solvents Corporation, New York City, for the Aciterge-OL and Alkaterge-O; to the Buffalo Electro-Chemical Company, Inc., Buffalo, New York, for the urea peroxide, ammonium persulfate, sodium percarbonate, magnesium peroxide, and sodium pyrophosphate peroxide; and to the Solvay Process Company, New York City, for the Chloramine-B. A more detailed report of the activity of the oxidizing agents will be published later with Dr. George A. Emerson, University of West Virginia Medical School, Morgantown, West Virginia.

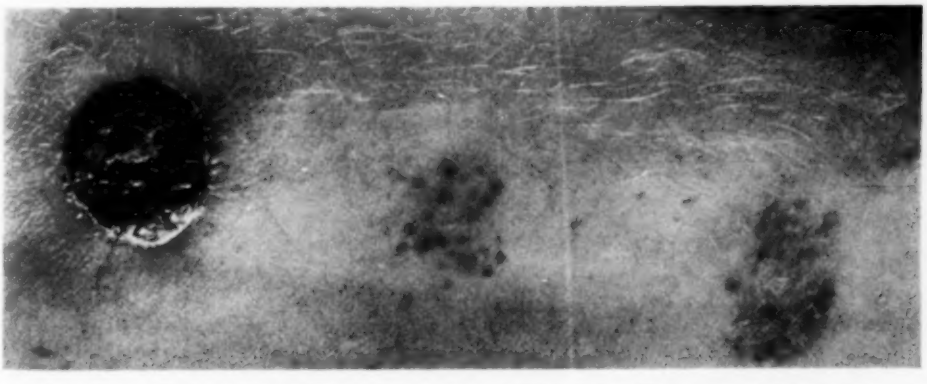

FIG. 1. Photograph of mustard gas burns on human arm (5 mg. applied directly). Untreated at left; hypochlorite treated in center, and soap suds treated at right.

gestions for "self-aid" in handling suspected war gas exposure are appreciatively received by the public because they are simple and sensible. Recently these suggestions in substance have been included in "official" recommendation.[12]

Recent statements of the Office of Civilian Defense indicate reasonable agreement with the point of view developed by us (Operations Letter No. 128, Office of Civilian Defense, May 15, 1943). We are grateful for the cordial coöperation of the Office of Civilian Defense in our efforts on the Pacific Coast last year and for many helpful suggestions in this report.

Some later experimental data on the comparison of methods of treatment for mustard gas exposure are given in tables 3 and 4, as well as in the full-size photograph.

Summary

War gases act on people economically, politically, and psychologically, as well as in direct biological ways. It is wise to offer all available information on war gases to the public in order to dispel ignorance, reduce fear, and prevent panic from their possible use against civilians.

Since mixtures of war gases are likely to be used, it is ridiculous to recommend protection to civilians on the basis of specific identification of any single war gas. It is much wiser to devise methods of protection for civilians against war gases that will take care of anything that may be suspected. Protection should also be devised against "nitrous fumes" from high explosives.

Although gas masks and special protective clothing are necessary for combatants, civilians may protect themselves against war gases without such expensive equipment. The most effective protection for civilians against war gases is to obey air raid rules. If the shelter is broken by bombing, and if war gases are suspected, a cloth soaked in baking soda solution or in diluted kitchen bleach solution, may be tied over the nose and mouth to breathe through. A solution of a teaspoonful of baking soda in a glass of water is most effective for washing irritated eyes, nose or throat. If splashes are suspected on the skin or clothes, clothing should be thrown out the window, splashes should be promptly blotted with cloths wet with kitchen bleach solution, and rinsed copiously with soap and water. If subsequent injury results, the management is symptomatic at a casualty station or hospital.

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DERMATOSES INCIDENT TO INDUSTRIAL AND DOMESTIC OCCUPATIONS*

By EVERETT S. LAIN, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

NATURE has provided the human body with an elastic, pliable, vital external covering, which we call the skin. The skin possesses five primary physiological functions and many secondary functions correlated with those of other organs. In this presentation we are more especially concerned with the protective powers of the thin external layer we call the epidermis. Histologically the epidermis appears lifeless, but when exposed to an environment of abnormal temperature, trauma, chemical or bacterial invasion, its wonderful power of protection seems almost unbelievable and appears to rival that of every other organ of the entire human economy. However, owing to inheritance of a certain less defensive type of skin or to long unfavorable environmental exposure, the limit of its tolerance may eventually be reached and beginning reaction in the form of eruptions becomes manifest.

During the present world wide conflict, when industrial activity demands speed and more speed, we may naturally expect carelessness and inadequate protection against health hazards.

According to Colonel Louis Schwartz [1] of the United States Public Health Service, occupational dermatoses now account for nearly 70 per cent of all industrial injuries. It is further estimated that the average time lost by each worker on account of industrial diseases totals about five weeks. When this time is converted into manpower hours, the total loss runs into many millions of dollars.

Therefore, scarcely a single Public Health or Industrial program has been presented during the past two years which has not devoted a large part of its time to the problem of Industrial Dermatoses.

Our United States Congress has, during recent years, wisely provided additional appropriations and a larger personnel for Public Health Service. Under the direction of Colonel Louis Schwartz, head of the Department of Dermatoses Investigation, Industrial Training Schools and Clinics have been organized in various parts of the country in order better to prepare physicians and safety engineers to combat this alarming loss of manpower which in a large measure is preventable. Before the advent of synthetic chemistry and advancing demands of modern civilization for multiple machines for rapid transportation and comfort both by land and air, the average physician was satisfied to be able to recognize common contact dermatoses caused by cosmetics, strong soaps, unslaked lime and cements. He was also familiar with the dry, erythematous or vesicular eruptions on the hands of the phar-

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macist or laboratory technician or over the unprotected hands, arms and face of the painter or furniture repairman.

With the advent of World War I, there was a sudden awakening in the field of both basic and synthetic chemistry with increasing interest and demand of the public for more and larger manufacturing establishments to supply the requirement of both private and military life.

It should be noted that not only have laborers who work in chemical, machine or industrial shops suffered skin injury from contact irritants, but domestics, housewives, and others who have accepted and used a new untested soap or cosmetic, or perhaps have purchased articles of clothing which have been treated with synthetic gums,[2] resins, or other chemicals in order to give better wearing qualities, luster and sales appeal, have likewise become affected. These goods are sometimes rushed into the market without proper precautionary skin testing.

Most petroleum distillates used as solvents or degreasing agents may be classified as possible skin irritants as well as many of the highly advertised, so-called labor saving chemicals such as water softeners, bleaches, etc., which are usually highly concentrated alkalies to which chlorinated products may have been added and which will under certain favorable conditions cause annoying erythematous, dry or exudative eruptions.

Major new industrial health problems of today have been suddenly thrust upon us by the demands for the building of hundreds of new and the revamping of thousands of old chemical or other research laboratories and manufacturing plants for the turning out of explosives, poisonous gases, ammunition, war machines, armament and air transportation. We may better understand this problem when we are reminded that according to reliable statistics, there are now more than 1,500 known general skin irritants classified as acids, alkalies, salts, anhydrides or solvents. Also, there are many known specific or primary skin irritants such as dyes for fabrics and shoes, photo chemicals, rubber compounds and plasticizers, insecticides, fungicides, explosives, certain cosmetics, several mineral and vegetable oils, and many natural or synthetic resins and waxes. It now appears that there can be no potent chemical formulated or routine protective measures instituted which will, under all conditions of exposure, prove entirely harmless for certain so-called sensitive or allergic types of individuals.

Notwithstanding the wisely supervised construction of hoods, ventilators, and the use of protective creams, aprons, sleeves and gloves, which are insisted upon by industrial physicians and safety engineers, the incidence of skin reactions is still high among older as well as the new and untested employees.

The medical profession has, in former years, concerned itself largely with curative measures, although now the industrial physician who can evolve successful protective measures against skin or other injuries is just as much in demand as the skilled mechanic who turns out a finished machine.

It should be remembered that refined petroleum products or distillates such as the kerosenes, naphthalenes, benzols, gasolines, carbon tetrachloride, and the alcohol groups used as solvents are all defatting agents and tend to lower skin resistance.

Without its natural oil, the skin is left in a dry condition susceptible to mechanical abrasions, chemical absorption or bacterial invasion through the epidermal gland ducts or hair follicles. According to United States Public Health Reports, cutting oils [3] are the most frequent cause of eruptions in machinists and metal workers. Industrial laboratories are striving to prevent bacterial infections caused by cutting oils, and greases, which by repeated use soon become contaminated by precipitates of septic foreign material such as dirt, metal filings and shavings. They have attempted to refilter and add sterilizing chemicals or antiseptics to these oils with only a small measure of success.

Employees in certain departments of industrial plants may unconsciously be exposed for long hours to injurious sprays of paints, vapors of soldering or welding chemicals which contain sodium fluoride and acids. New hazards are continuously being discovered with the introduction of new materials and chemicals.

Recently there have occurred many cases of a characteristic papulopustular eruption on the face and arms and sometimes over the bodies of splicers and welders of electric wires which are covered with a new fireproof, insulating, synthetic resin known as Halowax. Some of these workers have, through inhalation of vapors, also suffered serious liver damage.

Criteria for Diagnosis [4]

History. In no field of medicine is the taking of a careful history and an acquaintance with industrial chemistry more essential than in the care of industrial employees.

(*a*) First-appearance—reasonable period after beginning present work.
(*b*) Did eruption first appear over the unprotected areas?
(*c*) Have other fellow workers been similarly affected or does medical literature report other cases from similar exposure?
(*d*) Does removal of worker from present environment for a period of not less than one or two weeks improve his condition?
(*e*) What other possible contacts may occur at home or during their off hours?

Examination.

(*a*) Examine the entire skin surface of the stripped body, including feet, for fungus infection and the oral mucous membranes for possible evidence of non-industrial diseases.

(*b*) Note character of primary or first type of lesion, location, spread and changes which may have occurred from treatment.

(*c*) Is eruption worse over areas where contaminated or poorly laundered work clothes and perspiration may have been contributing factors?

(*d*) What water softeners or bleaching chemicals may have been used in laundering of work clothing?

(*e*) Is eruption of a bacterial type and does it cause any elevation of temperature?

(*f*) Finally, make patch tests with suspected irritant moistened preferably with perspiration.

Prevention. Most occupational dermatoses are preventable if qualified, medical supervisors and adequate mechanical protective devices are provided. Poisonous vapors and floating dust must be drawn away by inlets of fresh clean air and suction ventilators from overhanging hoods.

Removal of work clothes and shower baths immediately after work hours must be urged especially in certain hazardous departments.

Workers should, insofar as possible, wear impervious clothing, such as protective synthetic, rubberized aprons, sleeves, gloves and waterproof shoes.

In the cleansing of their hands, arms, face or bodies, workers must not use strong grit impregnated soaps or degreasing solutions which in some cases prove more injurious than the substance to be removed.

It is now known that workers suffering an occupational dermatosis may under proper treatment slowly develop complete immunity or be transferred to another department with perfect safety.

Many reliable manufacturing chemical laboratories have been striving to formulate non-irritating, protective creams, or film coatings, to be applied to the exposed surfaces of workers with some degree of success, though no universal skin application has yet been compounded which will furnish protection against all classes of hazards.

Several reliable drug manufacturing plants have, after careful research, placed on the market creams and film coatings designed to protect workers from each specific exposure. Such attempt is commendable and may eventually prove more successful.

Treatment. Early recognition of occupational dermatoses by a qualified industrial physician is tantamount to a shortened period of recovery. Treatment should consist first of removing from the skin insofar as possible the offending chemical or source of infection. Acute exudative eruptions usually demand first cooling, soothing, astringent wet packs.

If the dermatosis is of longer duration and has become chronic, internal medication designed to assist elimination of the toxic agent in addition to local bland, oily, protective and sometimes stimulating applications may be indicated.

In this discussion I have drawn largely from investigations and medical publications of Earl D. Osborne, Buffalo, Harry R. Foerster, Milwaukee, and John W. Downing, Boston.

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MILITARY DERMATOLOGY *

By Leon H. Warren, Major, M. C., A. U. S.

Military dermatology differs from civilian dermatology in the incidence and handling of skin diseases of military importance. The incidence of dermatoses is modified by the existence of larger groups in the military population, increased physical exertion, reduced sanitation, and restricted therapeutic facilities. In contrast to the average civilian family of three, the average military group consists of approximately 60 men. These larger groups must live in whatever environment the military situation demands. Even in barracks in the zone of the interior soldiers undergo greater physical exertion, perspire more freely, and have restricted facilities for bathing, laundry, and other sanitary measures. In the field where tentage is substituted for housing these facilities are still further restricted. During combat and the subsequent occupation of towns in which sanitary facilities have been disrupted, the reduced hygiene of the civilian population and of requisitioned living quarters creates additional skin hazards.

In warfare morbidity is more important than mortality, inasmuch as sickness produces noneffectives who require not only supplies but also the services of other personnel for their care. From a tactical standpoint, noneffectives constitute a greater disadvantage than actual losses. Military medicine must, therefore, concern itself more with reducing morbidity than with preventing mortality. Hence the emphasis in military medicine is primarily on preventive medicine.

Military dermatology is concerned with those skin diseases which cause the greatest number of noneffectives among military personnel. The skin diseases of military importance are not rare, foreign or tropical skin diseases, but are limited chiefly to a few of the common skin diseases, diseases which the general practitioner should be able to treat as competently as the specialist. The skin diseases of greatest importance in military medicine are found in the following categories:

1. Superficial fungous infections.
2. Parasitic skin diseases and insect bites.
3. Contact dermatitis caused by plants or chemicals.
4. Pyogenic skin diseases, including secondary bacterial invasion of fungous or other skin diseases.

The following admission and noneffective rates compiled by the Medical Statistics Division of the Office of The Surgeon General indicate the relative

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importance of all skin diseases in the Army and the relative importance of the most common skin diseases in military medicine.

Common military skin diseases	Admission rate per 1,000, Calendar Year 1941	Tentative Noneffective rate
Diseases of skin and cellular tissue	61.80	1.59
Ectoparasitic (excluding insect bites)	.85	.01
Scabies	2.52	.07
Contact dermatitis	10.40	.23
Pyodermas (ecthyma, furunculosis and impetigo)	4.91	.15

These statistics give the recorded incidence of skin diseases in the Army during the period of mobilization. Although these figures represent only a fraction of the actual incidence, they are significant because they indicate that over 6 per cent of the Army was actually hospitalized for skin diseases at some time during that period.

In the Army, skin diseases were formerly treated by internists on the medical wards, whereas syphilis and other venereal diseases were treated by urologists on the surgical wards. The Military Personnel Division of The Surgeon General's Office has classified those medical officers who are qualified in dermatology and syphilology. It is the policy of The Surgeon General's Office to assign at least one dermatologist to each hospital of 250 beds or larger, and two dermatologists to the larger hospitals. In most Army hospitals cases of skin diseases, syphilis, lymphogranuloma venereum and granuloma inguinale are treated by the medical service. The Bureau of Medicine and Surgery of the Navy Department has adopted the policy of assigning cases of skin disease and syphilis to dermatosyphilologists on skin and syphilis wards.

In the practice of military dermatology, especially in the field, treatment routines should be of single application type and should not require follow-up to make certain that they are effective. For example, in order to control pubic lice in the Army, ova are eradicated by shaving the pubic hair, rather than by applying ovicides and having to wait 12 days in order to make certain that the treatment is successful. Ideal treatments must in many instances be replaced by available treatments and by much improvisation necessitated by restrictions and uncertainties in supply. Less attention to aesthetic effect or to the patient's coöperation is necessary in the practice of military dermatology. Indeed, one should not have to depend upon the patient's coöperation for the success of treatment. In many instances self medication will be necessary. Medicaments selected for such cases must not be potentially irritant or harmful.

Superficial Fungous Infections

Dermatophytosis. The skin disease which causes most of the noneffectiveness in the tropics is athlete's foot. Although it was formerly assumed that the bringing together of large numbers of men favors the incidence and

spread of dermatophytosis, there is now a tendency to minimize the rôle of crowding as a factor in increasing the incidence of this disease. However, the problem of athlete's foot is of greater importance in military than in civilian life. In the Army, commands with an apparently low incidence of athlete's foot—low as long as troops remain in garrison without long marches—may develop a high percentage of disabling athlete's foot on an all-day march. In the Navy, tired, swollen feet and flare-up of dermatophytosis constitute a limiting factor during endurance runs in peace time and during cruises under forced draft in war time. It is difficult to detect cases of quiescent athlete's foot upon routine inspection prior to flare-up or to predict which cases will flare up. Heat and the friction of heavy boots cause flare-up in some cases but not in others. Furthermore, the degree of involvement necessary to disable a soldier does not have to be as great as that required to disable a civilian. A civilian during a flare-up of athlete's foot may be able to hobble around at intervals for relatively short distances and remain on the job, whereas the same amount of involvement in military personnel on prolonged marches or in the black gang in the engine room or boiler room aboard ship would be totally disabling. In the military services facilities for wet dressings—the treatment of choice in the acute stage—are unavailable except in hospitals and aboard the larger vessels of our Navy. This lack of treatment facilities handicaps the efforts of the medical officer to return the patient to duty.

Dermatophytosis includes both trichophytosis and epidermophytosis. Dermatophytosis and ringworm (tinea) are caused by superficially parasitic fungi which invade the keratin layer of the skin, hair, and nails. Heat and maceration in the body folds favor reproduction and invasion of the epidermis by fungi and later secondary invasion by bacteria. In the acute stage the lesions of the various types of dermatophytosis and ringworm are those of an acute, marginated dermatitis, with erythema, vesiculation, and weeping or exudation. Later the primary lesions become macerated, desquamative, and in some instances secondarily infected and pustular, causing a high percentage of disability when involving the feet. The latter stage sometimes develops into a focus of recurrent, disabling, erysipelatoid, streptococcic infection of the foot and leg. Other lesions include hyperkeratosis, lichenification (thickening and increased prominence of skin markings) caused by scratching, and chronic dermatitis or eczema.

Dermatophytid. In addition to localized primary involvement by the fungus itself, accompanying or following the deeper type of primary lesion known as kerion or honeycomb ringworm there may occur generalized sensitization eruptions known as dermatophytids. Intradermal trichophytin tests and identification of the fungus by direct microscopic examination of scrapings from the primary focus or by culture are necessary in order to establish a diagnosis of dermatophytid. The dermatophytid may assume various forms but is usually papular or vesicular. Uncomplicated types

undergo spontaneous remission upon response of the primary focus to treatment. Flare-up of dermatophytids usually coincides with recurrence or exacerbation of the primary lesion, caused in most instances by heat and possibly in some instances by increased nervous tension.

Dermatophytosis of the Hands and Feet. In the differential diagnosis of the primary lesions of dermatophytosis of the hands and feet, contact dermatitis must be ruled out. Although there are no absolute morphologic criteria for clinical differential diagnosis between dermatophytosis and contact dermatitis, the former is usually characterized by a more localized, marginated or sharply demarcated patch. Contact dermatitis tends to involve both hands uniformly, in contrast to a primary focus of dermatophytosis which tends to involve only one hand and to be limited to a single patch. Dermatophytids usually involve the lateral borders of the fingers, but may involve the palm and must be differentiated from pompholyx (dyshidrosis) and contact dermatitis.

Prophylaxis. For the prophylaxis of dermatophytosis, Army issue foot powder is recommended. This consists of 2 per cent salicylic acid, 6 per cent boric acid, 1 per cent desiccated alum, 3 per cent zinc stearate, 10 per cent starch, and 78 per cent powdered talc. Powder, by increasing the surface area of the skin, promotes evaporation, cooling, and drying, and thus counteracts the effect of heat and maceration which favor fungous infections. The feet should be washed frequently, dried thoroughly, and the socks boiled or rinsed in sodium or calcium hypochlorite solution containing 20 parts per million of residual chlorine. In addition, an aqueous solution of sodium or calcium hypochlorite containing 50 to 100 parts per million of residual chlorine, tested at daily intervals, should be used in a shallow footbath in the runway leading to shower rooms. It should be noted that sodium hypochlorite is a bleach and is not the sodium thiosulfate used as a photographic "hypo." Sodium thiosulfate has little fungicidal action in vitro. Any prophylactic value attributable to the latter may be due to the fact that it forms copper salts upon standing in footbath containers made of copper.

Treatment. There are no magic formulae and few specific treatments in dermatology. There are only logical lines of approach and many equally good formulae, good if used in the appropriate stage of a skin disease. Failure to secure arrest of the acute stage of dermatophytosis and to prevent recurrence in the chronic stage is due to overtreatment in the first instance and to lack of persistence in the latter. The acute stage should be treated simply as an acute dermatitis, without attempts at fungicidal action. Wet dressings or soaks of a saturated aqueous solution of boric acid (four teaspoonfuls of the powder in one pint of water), or Burow's solution of aluminum acetate diluted 1:16 (two tablespoonfuls of Burow's solution in one pint of water) are recommended.

The pustular type should be treated with soaks or compresses of 1:2,000 potassium permanganate solution. Sulfonamides by mouth or combined in

a foot powder may be indicated in some instances, particularly in the treatment of secondary cellulitis of the leg.

After most of the vesiculation has subsided, it is safe to proceed with fungicidal powders, solutions, or ointments.

1. Powder: Army issue or similar foot powder.

2. Keratolytic and fungicidal solution: 6 per cent salicylic acid and 12 per cent benzoic acid in alcohol.

3. Dye solution: Castellani's paint, consisting of 1 per cent boric acid, 5 per cent acetone, 10 per cent resorcinol in a sufficient quantity of Ziehl's carbol fuchsin solution. This solution helps control bacterial infection and should be used instead of ointments in the tropics.

4. Ointment: Whitfield's ointment, consisting of 6 per cent salicylic acid and 12 per cent benzoic acid in petrolatum. When in doubt as to whether the acute symptoms have subsided, that is, whether vesiculation has disappeared, it is always safer to begin with half strength Whitfield's ointment and increase this to full strength after five to seven days.

Prevention of Recurrence. Two causes of recurrence are failure to persist in treatment after the visible signs of infection have subsided and failure to prevent reinfection by prophylactic measures, including attempts to disinfect articles worn or handled by the patient. The fungicide recommended for disinfection of leather goods consists of an aqueous solution of sodium or calcium hypochlorite containing 20 parts per million of residual chlorine.

Ringworm of the Groin and Axilla. There are two types of ringworm of the groin: the more common tinea cruris, and the less common erythrasma. These fungous infections may also involve the axilla and must be differentiated from simple chafing or intertrigo. Intertrigo (chafing) may be caused by heat, maceration, and friction or may be caused by infection with yeast-like fungi in the body folds. Intertrigo is more inflammatory, redder, and more limited to the body folds, whereas ringworm tends to spread away from the body folds, to be less inflammatory, and to have an advancing margin with clearing and often hyperpigmented center, with occasional minute vesicles in the finely scaling border. Erythrasma, in addition, has a peculiar dull brownish-red pigmentation which is clinically suggestive of the diagnosis.

Treatment. In the treatment of ringworm of the body folds, particularly when the scrotum is involved, the use of irritants such as iodine or the use of heavy powders which plug the follicles should be avoided.

1. In the acute stage use compresses of a saturated aqueous solution of boric acid, or 1:2,000 aqueous solution of potassium permanganate in secondarily infected cases.

2. When vesiculation has subsided, use an ointment consisting of 1 per cent salicylic acid and 3 per cent ammoniated mercury in petrolatum. If the ointment is too heating, substitute half strength Whitfield's solution consisting of 3 per cent salicylic acid and 6 per cent benzoic acid in alcohol, or use Castellani's solution.

3. On the scrotum and in cases in which an ointment is not tolerated, use either Castellani's solution or the following modification of Burow's lotion: 12 per cent Burow's solution of aluminum acetate, 2 per cent resorcin, 4 per cent boric acid, 12 per cent chalk, and 25 per cent witch hazel water in a sufficient quantity of water.

Prevention of Recurrence. Underwear should be boiled or rinsed in a solution of high test hypochlorite if bleaching is not objectionable.

Parasitic Skin Diseases

Parasitic skin diseases may be divided into two categories: (1) those caused by permanent or endoparasites such as scabies and other mite infections; and (2) those caused by temporary or ectoparasites such as pediculosis of the scalp, body and pubic area. Of chief military importance among the latter are infestation by lice, jiggers, chiggers (redbugs), phlebotomi ("sandflies"), ticks, bedbugs, fleas, and fly larvae.

Scabies. This disease has increased from an incidence of 2.5 per thousand in the calendar year 1941 to as high as 60 per thousand in certain theaters for limited periods in 1942. The name, scabies, is derived from the Latin verb meaning to scratch and the lesions are spread by scratching. The female itch mite burrows in the epidermis, lays eggs, and deposits feces. Both eggs and feces are irritant and may be responsible for the granular or micropapular secondary lesions. The primary lesion, of lesser importance than the distribution in the diagnosis of this disease, is a papule or vesicle. In some instances a characteristic lesion known as a burrow or gallery is present. The primary lesions undergo secondary pustule formation, with spread in scratch marks and denudation of the tops of the lesions by scratching. In some instances the appearance is complicated by secondary inflammation of the skin, caused by hypersensitivity to sulphur used in the treatment of the disease. In some cases the primary lesions become secondarily infected.

As previously indicated, the type of lesion is relatively unimportant in the diagnosis of scabies. The chief diagnostic feature is the distribution or localization on the thin-skinned areas of the body. The sites of predilection are the webs of the fingers, wrists, axillary folds, nipples, beltline, buttocks, groin, thighs, shaft, and glans penis. Except for spread in scratch marks, producing a linear configuration, there is no characteristic configuration in scabies. The lesions do not tend toward grouping, nor to confluence, but on the contrary are discrete and disseminate. Lesions rarely occur on the palms or face in adults. In view of the predilection for thin-skinned areas, it is strange that the eyelids are exempt, particularly since there is ample opportunity for transferrence to this site by rubbing the lids.

Treatment. The most readily available treatment is the time-honored sulphur ointment. This is effective in 99 per cent of cases, provided the patient is hospitalized for five days. Use 10 per cent precipitated sulphur in

a base of benzoinated lard, rather than in petrolatum. Prescribe three ounces of the salve and give detailed instructions for its use. Lack of understanding of these directions by the patient accounts for most of the failures. The remainder of failures are mainly cases in which the patient becomes reinfected. Have the patient take a warm soap and water bath before retiring, then after the bath rub from neck to toes with the salve, with particularly careful application to the sites of lesions. The next two mornings and evenings the application of salve is repeated without bathing. On the third morning the patient is instructed to take a warm soap and water bath, and to change underclothing, bed linen, and pajamas and boil the dirty linen and clothing in order to prevent reinfection. The application of sulphur ointment is then discontinued for at least four days. If there is recurrence of the lesions, the salve is applied for one week to the lesions only. If this fails to check the disease, after having waited four days the original course of antiscabetic treatment is repeated. In order to control scabies, one of the main causes of noneffectives to date, there is needed a treatment which will require only a single application in the field, rather than hospitalization for a minimum of five days. It is possible that this need will be met by the recently proposed adoption of the one or two application treatment with benzyl benzoate lotion. This preparation now appears to be equal to sulphur ointment in efficiency and superior to the latter in that benzyl benzoate is less apt to cause dermatitis and requires fewer applications.

Insect Bites. A combined insect repellent and insecticide, effective on both crawling and flying insects, would fill a definite need in military medicine. At present the Army has an effective insecticidal powder for use against crawling insects such as ticks, chiggers (redbugs), lice, etc. For the destruction of lice this powder is dusted lightly into the seams of the clothing at weekly intervals. For the prevention of chigger (redbug) and tick bites, the powder is dusted along the belt-line and inner side of clothing of the lower extremities, including socks and shoes. When sleeping on the ground, soldiers should protect blankets from infestation with crawling insects by lightly dusting the bedding with the powder at weekly intervals. Army repellents for mosquitoes and other insects include Eveready ("612") and dimethyl phthalate. As an insecticidal spray, a standard preparation containing pyrethrum or pyrethrum plus an activator, is used.

The recognition of insect bites sometimes constitutes a rather difficult problem in the differential diagnosis of skin diseases. In general, insect bites tend to assume the form of a papule or vesicle with central punctum on an urticarial base, distributed along the belt-line or uncovered portions of the lower extremities. Flea bites tend to occur in a zigzag linear configuration where the insect has moved from one site to another during feeding.

Flea Bites. The fleas which bite man are cat and dog fleas, human fleas, rat fleas, and the tropical sand flea (*Tunga penetrans*). In addition to constituting a nuisance, rat fleas transmit endemic typhus and bubonic plague.

Rat fleas are best controlled by killing rats with methyl bromide or hydrocyanic acid gas. Dog and cat fleas may be destroyed by the application to the animal of a powder containing derris extractives in talcum powder. The tropical sand flea (chigoe) may be destroyed by the application to the premises of insecticides such as naphthalene. Dimethyl phthalate is recommended as a repellent.

Pediculosis. The body louse is important as a carrier of *Rickettsia prowazeki,* the causative agent of epidemic typhus. Lice may also carry the causative organisms of trench fever and relapsing fever. In addition, they are an important factor in the morale of troops. Since few cases are hospitalized, statistics on the incidence of louse infestation are incomplete.

Infestation with lice produces some of the longest scratch marks seen in any skin disease. The scratches are parallel, distributed over the extremities and trunk, with the exception of the interscapular area, and are followed by hyperpigmentation caused by the resultant stimulation of melanin formation. Except for the transitory tache bleuatre or bluish spot sometimes produced by the bite of the louse, there are no characteristic or primary lesions. In some cases of louse infestation there is malaise, low-grade fever, and a morbilliform eruption on the trunk.

There is need for a combined delousing and fungicidal agent. The Army insecticidal powder mentioned previously is effective against lice but is not a fungicide. The recently developed fumigation chamber for delousing clothing utilizes methyl bromide gas as a pediculicide and ovicide. This gas, however, is not a good fungicide. The older method of delousing by use of the steam chamber also kills fungi but is hard on clothing and leather. Dry heat is not as injurious as moist heat to clothing but will not penetrate readily. Lice ova may be removed from the patient's body by clipping or preferably by shaving the hair, followed by a hot soapy bath. In cases in which the hair is not removed, nits should be loosened by the application of vinegar or 10 per cent acetic acid solution, followed by the application of 25 per cent kerosene in water, thorough combing and shampoo. If the above medicaments are not available, pediculosis capitis may be treated by the application of Army insecticidal powder, followed in 48 hours by thorough combing and shampoo.

Contact Dermatitis

In order to confirm a diagnosis of contact dermatitis of plant or other origin, patch tests with the suspected irritant are requisite. However, in the majority of instances such confirmation is impracticable and unnecessary for the successful treatment of cases. Furthermore, there is a risk involved in the performance of such patch tests after an interval of 10 days from the onset of dermatitis has elapsed, the risk that a systemic hypersensitivity has developed in the meantime and that patch testing may then not only elicit

flare-up of the original site of inflammation, but also produce a more generalized allergic dermatitis.

Inflammation of the skin limited to exposed areas is suggestive of contact irritant origin. An element of diffuse swelling underlying an erythema with or without tiny vesicles is important in the diagnosis of acute contact dermatitis. Vesiculation may develop into progressively larger lesions which become confluent and form blebs or bullae. Another feature suggestive of the diagnosis of contact dermatitis is the spread of lesions in scratch marks or the development of a long chain of vesicles or linear bleb.

Treatment. Use compresses or soaks of a saturated aqueous solution of boric acid, or a 2 to 5 per cent aqueous solution of tannic acid in the acute, weeping stage, together with calamine lotion. Later, powder should be applied in the form of Lassar's paste.

The treatment of contact dermatitis caused by chemical warfare agents constitutes a highly specialized branch of military dermatology. Owing to the classified nature of much of the information on this subject, this cannot be included in this discussion.

Pyogenic Skin Diseases

Skin diseases of pyogenic origin are more common under conditions of reduced sanitation. In the tropics, furunculosis, impetigo, ecthyma, and other pyodermas are caused by lowered systemic resistance to pyogenic infection, possibly resulting from vitamin deficiencies, and by lowered skin resistance resulting from damage to the skin. This damage is produced by maceration caused by wearing too much clothing or by inability to keep the skin dry, as well as by trauma resulting from having to push through the jungles on military expeditions. Heat and low economic status produce pyodermas among natives. Heat and the reduced sanitation necessitated by field conditions during warfare produce pyodermas among soldiers in the tropics. The training in hygiene and sanitation received by troops in the temperate zone must be constantly emphasized and enforced when these troops enter the tropics. The skin must be kept clean and dry and antiseptics applied promptly to minor lacerations and scratches. Sleeping on the ground should be avoided. Hammocks should be used and clothing should be washed frequently, daily if possible.

Tropical Ulcer. This should be termed tropical ulcers, since no single cause has been discovered. Some of these are pyodermas, whereas others are ulcerative granulomas such as yaws or syphilis. Tropical ulcer should not be confused with oriental sore (cutaneous leishmaniasis). Lesions of the various tropical ulcers are usually marginated ulcers of the extremities. For their treatment 5 per cent ammoniated mercury ointment or Castellani's solution is recommended. When these are not available or when a drying effect is desired, use soaks or compresses of 1 : 2,000 aqueous solution of potassium permanganate.

Summary

Military dermatology is concerned with a few of the common skin diseases and of contact dermatitis caused by chemical warfare and other agents. These diseases are in most instances treated by medical officers who are general practitioners rather than by dermatologists. Treatment routines should be of single application type, require little attention to aesthetic effect, should not depend upon the patient's coöperation, and should not require follow-up. In situations where self medication is necessary, medicaments should not be potentially irritant.

THE RÔLE OF CONGESTIVE HEART FAILURE IN THE PRODUCTION OF THE EDEMA OF ACUTE GLOMERULONEPHRITIS *

By JOHN S. LADUE, M.D., PH.D., *New Orleans, Louisiana*

CONGESTIVE heart failure has long been recognized as a distressing complication of acute glomerulonephritis,[1] but only recently has the frequency of this complication been appreciated.

Murphy [2] reports cardiac insufficiency in 17 per cent of 94 cases, Marcolongo [3] in 40 per cent of 80 cases, Ellis [4] in 20 per cent of 100 cases, Master [5] in 33 per cent of 24 cases, Rubin [6] in 25 per cent of 55 cases, and Whitehill [7] in 71 per cent of 138 cases. Several case reports conclusively demonstrating the occurrence of congestive heart failure during acute glomerulonephritis have been published.[8, 9, 10]

Various explanations of the cause of this congestive heart failure have been advanced, but two have received major consideration by most investigators. Since hypertension is an almost constant finding in such patients, its etiologic importance is generally acknowledged. However, Levy [11] and Murphy [2] have each reported an instance of cardiac enlargement and cardiac failure in the absence of significant hypertension. Whitehill and his associates [7] have observed that congestive heart failure may appear before the onset of hypertension, but variations in blood pressure measurements are not infrequently seen early in the disease. There is only a rough correlation between the severity of the congestive heart failure and the degree of hypertension. Many patients may have marked hypertension and cerebral symptoms but no heart failure, whereas other patients may have only a moderate elevation of blood pressure and rather severe myocardial insufficiency. There is no good evidence that the "myocardial factor" is due to a myocardial lesion, although Franke [12] and Jungman [13] noted diffuse mottling of cardiac muscle fibers with fat droplets in patients dying of acute glomerulonephritis during the first World War. That myocarditis is frequent in patients dying of scarlet fever [14] is of doubtful relevance. No constant changes are seen in the hearts of patients dying of acute glomerulonephritis who also have congestive heart failure.[15] If the concept that glomerulonephritis is a generalized capillary disease [16] were accepted, it would be easy to assume that functional damage resulting from arteriolar or capillary constriction (causing poor blood supply to the heart) plays a part in the myocardial weakness.

Since the vast majority of patients who have congestive heart failure complicating acute glomerulonephritis also have peripheral edema,[2, 4, 6, 7] it

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seemed worthwhile to attempt to correlate the appearance and disappearance of edema with the presence or removal of congestive heart failure.

Some investigators [17] ascribe the edema of acute glomerulonephritis to increased capillary permeability, basing their belief upon the finding of more than 1 per cent protein in the edema fluid, but recent investigators,[18] using a different technic for obtaining edema fluid, have failed to find a higher protein content than that present in edema fluid due to congestive heart failure or to venous obstruction. Other workers [19] believe that the edema of acute glomerulonephritis is partly explained by a lowering of the blood proteins and emphasize diminution in the albumin globulin ratio. However, it is probable that changes in blood proteins are too slight to produce enough decrease in the osmotic pressure of the blood serum to effect a shift of fluid from the blood vessels to the tissue spaces.

Method of Study

From December 1941 to February 1943, 12 patients were admitted to the Louisiana State University medical service of Charity Hospital with acute glomerulonephritis complicated by peripheral edema. All were studied according to the following plan.

Patients were placed upon strict bed rest and given no medication except magnesium sulfate to control convulsions. Four patients were given a low protein, low salt diet; four a high protein, low salt diet; and four the regular house diet. There was no restriction of fluids, but the intake and output were charted. Daily measurements of the venous pressure, circulation time, blood pressure, weight, and degree of pulmonary, liver or peripheral edema were recorded. Frequent teleroentgenograms and electrocardiograms were made. The urine was examined at least twice a week and blood urea and phenolsulfonphthalein excretion tests were done. On one patient, the vital capacity was measured every other day. The heart area and diastolic heart volume were determined from the teleroentgenograms according to the method of Keys and Friedell.[20] It was possible to secure edema fluid from two patients and total protein determinations were done on these fluids. Blood proteins and albumin globulin ratios were determined for each patient.

Results

Two of the patients were white males, four were colored females and six were colored males. One colored female was 29 years old; the rest of the patients were between the ages of 5 and 16.

Ten of the 12 patients had had an upper respiratory infection with cough, coryza and sore throat 10 to 21 days before the onset of their symptoms of glomerulonephritis, but in two patients no history of a preceding infection could be elicited.

Swelling of the face and legs was the chief complaint except in one child who was brought into the hospital because of convulsions. Nausea and vomiting occurred once and headache twice. Seven patients complained of dyspnea and orthopnea on admission, and in three others it was noted on physical examination.

The neck veins were frequently engorged and râles were heard at the bases of both lungs in nine patients. Pleural effusions were encountered in four patients. The heart was markedly enlarged in eight patients and moderately enlarged in the remainder. The apical impulse was forceful in all patients, and a systolic thrill was felt in three. The heart rate was above 110 in all but two instances. A systolic gallop rhythm was heard in four patients, but no other abnormalities in rhythm were encountered. The pulmonic second sound was louder than the aortic second sound in the hearts of 11 of the 12 patients. The diastolic blood pressure was above 100 mm. Hg at some time during the first two days in every instance; the systolic blood pressure was 190 mm. Hg or more in five patients, but was 130, 135, 138, 145, 150, 165 and 180 in the remainder. The liver was enlarged in seven patients and ascites was noted twice.

The eye-ground findings were of interest. In two patients arteriovenous nicking was the only finding; in five patients it was associated with local lumen attenuation. In one patient a few pin point hemorrhages, as well as arteriovenous nicking and arteriolar spasm, were seen.

Hematuria was always present on admission and persisted until discharge in a few patients. Albuminuria was present in 10 patients and cylindruria in six. Elevation of the blood urea content was noted twice and in each instance the level fell to normal when the patient became compensated. The same two patients had a transient lowering of phenolsulfonphthalein excretion to 55 per cent which rose to 70 per cent or more before discharge.

Each patient's course is presented in chart form and for convenience in discussion patients are referred to by their chart numbers. The charts show in detail the changes in blood pressure, venous pressure, circulation time, weight, edema and diastolic heart size observed from the time of admission until well after the disappearance of congestive heart failure.

Using the severity of heart failure as a basis for separation, the patients fall into three groups. Group I, patients 1, 2 and 3, had no symptoms of congestive heart failure except edema, although the venous pressure was elevated in all. In Group II, patients 4 to 8 inclusive had, in addition to edema and elevated venous pressure, moderate to marked dyspnea and orthopnea. Patients 9 to 12, comprising Group III, had such severe signs and symptoms of congestive heart failure that the administration of digitalis was thought necessary.

In Group I, the circulation time was above normal only in patient 2. A drop in blood pressure preceded the fall of venous pressure and disappearance of edema in all three patients, but in patients 2 and 3 the blood pressure was

nearly normal before the venous pressure fell to 10 cm. of water (upper level of normal).

Teleroentgenograms taken on admission and after signs of congestive heart failure had disappeared showed a decrease in the diastolic heart volume in patients 2 and 3 of 95 c.c. and 82 c.c. Roentgenograms for comparison of the heart size at different intervals were not made for patient 1, but a decrease of 1.1 cm. in the transverse diameter of the heart was noted within three days as judged from percussion of the heart. Diuresis and weight loss occurred over the critical period as indicated in the charts. Hematuria, as might be expected, was the last abnormality of the disease to disappear in these patients. Table 1 gives the time of occurrence of all these circulatory changes as well as the values for the blood proteins and the albumin globulin ratio.

TABLE I

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group I. Blood protein levels and albumin globulin ratios are also given.

Pt.	Age	Days for			Decr. in D.H.V. in c.c. & T.D. in cm.			Final Decr. in D.H.V. in c.c. & T.D. in cm.			Blood Proteins	
		Initial drop in B.P.	V.P. to fall to 10 cm.	Fall in Wt.	T.D.	D.H.V.	Days	T.D.	D.H.V.	Days	Total	A/G
1	11	1	2	8	1.1	*	3	—	*	—	5.81	1.5/1.0
2	6	3	5	8	0.1	95	6	—	95	6	7.1	1.1/1
3	12	4	6	9	2.2	82	11	2.2	82	11	5.5	1.8/1

In Group II, the venous pressure was elevated in every instance and rose further upon right upper quadrant pressure, but none of the patients had prolonged circulation time. In all but patient 4, an initial fall in blood pressure slightly preceded the clearing of congestive heart failure and the fall of venous pressure to 10 cm. of water or lower, but the exact time relations are not as clear cut as in the first group of patients. In patients 4, 5, 6, 7, and 8, a significant decrease in the diastolic heart volume (192 c.c., 46 c.c., 118 c.c., 17 c.c., and 155 c.c. respectively) was found at the time compensation was considered complete. Patient 7 had an additional teleroentgenogram taken two weeks after compensation was complete; at this time the diastolic heart volume had diminished by 85 c.c. Figure 1 shows teleroentgenograms of patient 8. Progressive decrease in diastolic heart volume is apparent, as is clearing of the pulmonary congestion. Weight loss and diuresis during the critical periods are apparent from a glance at the charts. Albuminuria and cylindruria were more pronounced in this group but hematuria persisted for approximately the same length of time as in Group I. Table 2 summarizes the data just discussed for Group II and gives the values of the blood proteins and albumin globulin ratios.

In Group III, three of the patients had ascites and pleural effusions in addition to findings of marked edema, dyspnea, orthopnea, liver engorge-

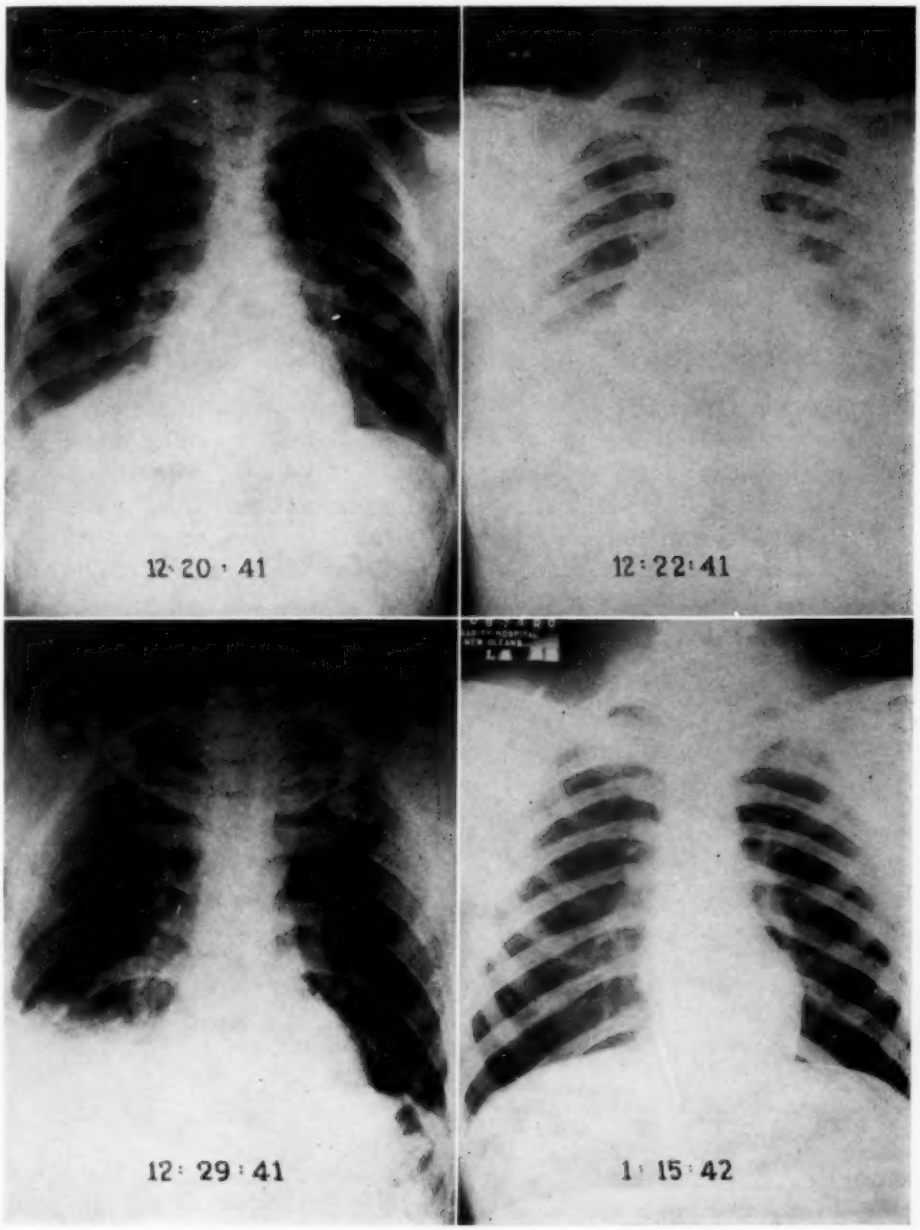

FIG. 1. Teleroentgenograms from patient 8 showing progressive decrease in heart size. Reading across, on the fifth day the diastolic heart volume was 1,010 c.c., on the seventh day 855 c.c., on the 14th day 691 c.c., and on the 24th day 678 c.c.

TABLE II

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group II. Blood protein levels and albumin globulin ratios are also given.

Pt.	Age	Days for			Decr. in D.H.V. in c.c. & T.D. in cm.			Final Decr. in D.H.V. in c.c. & T.D. in cm.			Blood Proteins	
		Initial drop in B.P.	V.P. to fall to 10 cm.	Fall in Wt.	T.D.	D.H.V.	Days	T.D.	D.H.V.	Days	Total	A/G
4	5	10	6	10	1.7	192	24	2.8	242	82	7.35	1.6/1.0
5	7	4	6	7	1.4	46.0	35	—	46.0	35	7.55	1.1/1.0
6	10	5	9	10	0.3	118	4	3.0	118	12	7.10	1.6/1.0
7	10	3	3	4	0.2	17	6	0.2	85	14	7.00	1.7/1.0
8	16	10	11	13	2.5	155	7	2.9	332	19	6.85	1.2/1.0

ment and pulmonary râles. One of the patients was given Cedilanid intravenously; three took usual amounts of folia digitalis * orally; and all received maintenance doses of 0.05 to 0.1 gram of folia digitalis daily.

In patients 9, 10, and 11, it is interesting to note that the signs of congestive heart failure disappeared and the fall in venous pressure occurred before any significant alterations in blood pressure were observed. The blood pressure in patient 12, who had mitral stenosis, fell before failure dis-

TABLE III

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group III. Blood protein levels and albumin globulin ratios are also given.

Pt.	Age	Days for			Decr. in D.H.V. in c.c. & T.D. in cm.			Final Decr. in D.H.V. in c.c. & T.D. in cm.			Blood Proteins	
		Initial drop in B.P.	V.P. to fall to 10 cm.	Fall in Wt.	T.D.	D.H.V.	Days	T.D.	D.H.V.	Days	Total	A/G
9	8	5	2	10	2.7	100	67	3.5	202	111	6.1	1.1/1.0
10	16	15	10	10	0.5	118	9	2.3	226	26	7.20	1.8/1
11	29	11	18	18	1.5	357	49	1.5	357	49	6.04	1.0/1.06
12	9	4	3	5	1.0	*	4	—	—	—	5.91	1.1/1.0

B.P.—blood pressure in millimeters of mercury
V.P.—venous pressure in centimeters of water
Wt.—weight in pounds
T.D.—transverse diameter of the heart
D.H.V.—diastolic heart volume
A/G—albumin-globulin ratio

appeared. In this patient, the mild attack of acute glomerulonephritis probably precipitated the severe congestive heart failure. The diastolic heart volume of patient 10 diminished 118 c.c. before compensation was complete. Patients 9 and 11 did not have roentgenograms taken until 67 and 49 days after disappearance of the signs and symptoms of heart failure, but at this time a decrease in the diastolic heart volume of 100 c.c. for patient 9, and

* One Hatcher-Brody cat unit of folia digitalis was given for each 10 pounds of body weight as a digitalizing dose.

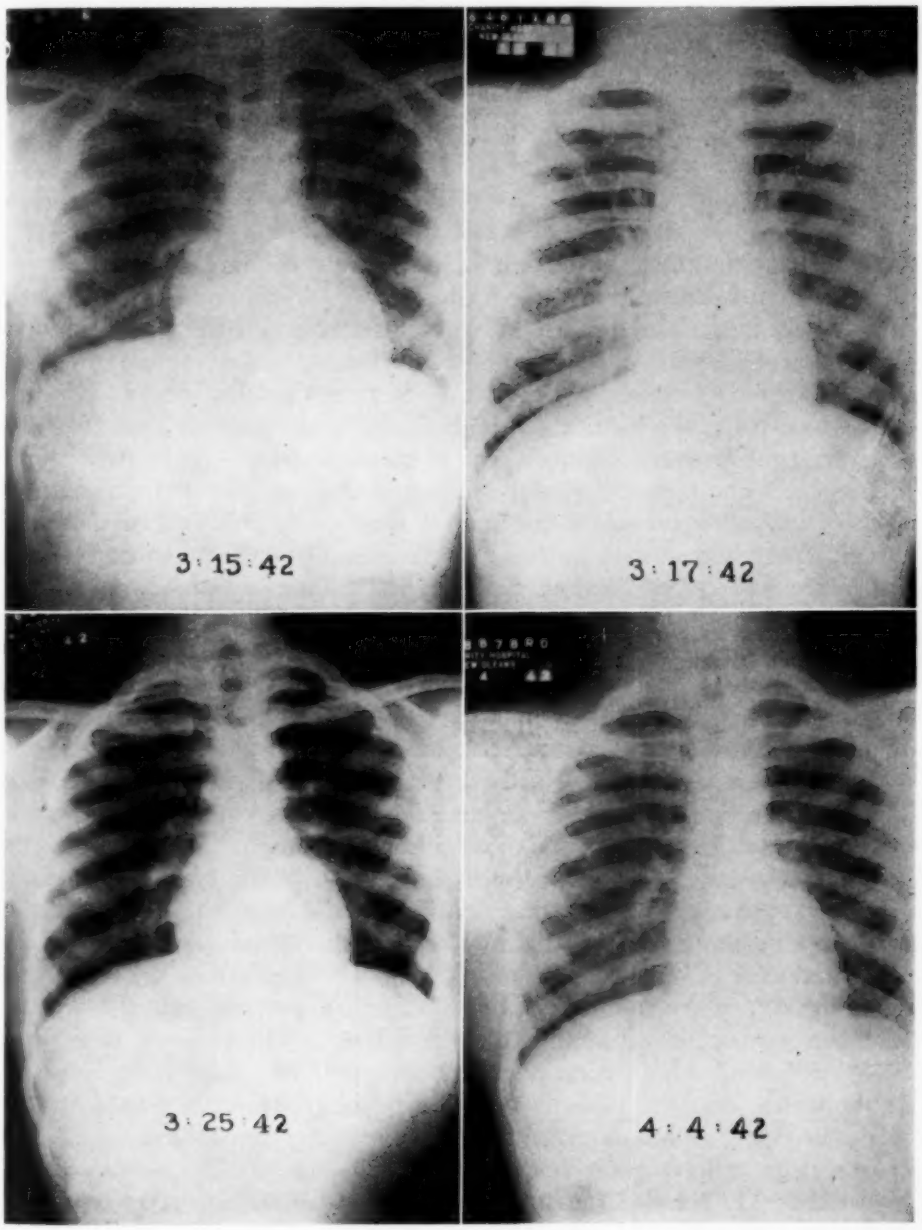

FIG. 2. Teleroentgenograms from patient 10, who was given digitalis. These show progressive decrease in the diastolic heart volume which was 907 c.c. on the first day, 912 c.c. on the third day, 794 c.c. on the ninth day and 686 c.c. on the 26th day.

357 c.c. for patient 11 had taken place. Figure 2 shows changes in the heart size and pulmonary congestion in patient 10. The transverse diameter of the heart of patient 12 had decreased 1.0 cm. in three days, according to a careful physical examination. Table 3 shows the time relationship of the circulatory changes just described and gives the values of the blood proteins and the albumin globulin ratio for each patient.

Discussion

There appears to be a close correlation between the time of disappearance of congestive heart failure complicating acute glomerulonephritis and the time of occurrence of the initial fall in blood pressure, since the fall in blood pressure preceded the disappearance of the signs and symptoms of heart failure in seven of the eight patients who were not given digitalis. In three of the four patients who were digitalized, the blood pressure remained high for some time after the establishment of compensation. These facts appear to strengthen the suggestion of the etiological importance of the blood pressure in the pathogenesis of the heart failure of acute glomerulonephritis, since it is well known that digitalis acts to decrease the diastolic heart volume and increase the mechanical efficiency of the failing human heart whatever the cause of the failure.[21] The fact that the fall in blood pressure usually precedes the disappearance of the symptoms and signs of congestive heart failure appears to support the following explanation of the mechanism by which cardiac compensation is initiated. When the blood pressure falls, the amount of work that the heart must do is lessened and this permits, according to Starling's law of the heart, a decrease in the diastolic heart volume. This decrease in diastolic heart volume is one of the earliest of a chain of events observed in compensation of a failing heart lung preparation [21] and has been recently described in a study of the failing human heart.[22] These investigations have also shown that relatively small increments in the cardiac output over a short period of time will reduce the pulmonary congestion and peripheral congestion (as indicated by a fall in the venous pressure), culminating in a return to normal of all the circulatory measurements.

Since cardiac output studies were not done in our patients, there is no evidence that all these changes actually occurred, but the striking similarity of the course of these patients with heart failure consequent to acute glomerulonephritis to that of patients recovering from heart failure due to other causes suggests that similar mechanisms may be involved.

In tables 1, 2 and 3 measurements of the diastolic heart volume made within two weeks after compensation was established (the third teleroentgenogram) showed a further decrease in the diastolic heart volume of patients 6, 8, 9, and 10. This subsequent additional decrease in diastolic heart volume has also been noted in patients having congestive failure due to other causes.[22] The finding of low to normal circulation times in all but one of these patients with acute glomerulonephritis, despite their elevated venous

pressure, has not been reported before. This has been noted in heart failure due to beriberi and has been ascribed to diminished capillary resistance. No explanation, however, is offered for the decreased to normal circulation time seen in our patients. The pulmonic second sound was accentuated in 11 of the 12 patients, suggesting the possibility of pulmonary hypertension in addition to the proved systemic hypertension. That this accentuation was probably due to pulmonary hypertension was attested by the fact that in four patients whose heart failure disappeared before the blood pressure fell, the pulmonic second sound remained markedly accentuated until the fall in blood pressure occurred.

Elevation of the venous pressure results in an increase in the capillary filtration pressure, and this appears to be the probable mechanism of the formation of the edema seen in these 12 patients. In no instance were the blood proteins decreased enough to account for the edema on the basis of a diminution in the osmotic pressure.

Swelling about the eyes was, as is usual, prominent in these patients. Sodeman and Burch [23] found the tissue pressure of the infraorbital region less than that of any other subcutaneous tissue, and it is reasonable to expect fluid to accumulate where the resistance is least in any instance of a generalized elevation in the capillary filtration pressure.

We obtained tissue fluid for protein analysis from two of our patients. In one, 0.7 per cent protein was found, and in the other, 2 per cent. In the latter, only a small amount of fluid was secured and that contained red blood cells. It is desirable to discard the fluid obtained during the first two to six hours to avoid mixing with blood or with fluid escaping from the capillaries injured by the placing of the Southey tubes.

Contrary to the findings of earlier investigators,[17] Warren [18] and Koschnitzke [18] failed to find a high protein content in the edema fluid secured from patients with acute glomerulonephritis. Edema fluid with a high protein content might be expected if the edema were explained upon the basis of increased capillary permeability. Some workers suggest that the damaged kidneys of patients with glomerulonephritis are unable to excrete salt and that the edema is simply a salt retention edema, but cite no supporting evidence. Our patients had a prompt diuresis when their heart failure began to clear following the fall in blood pressure.

Electrocardiographic abnormalities have been reported in from 20 to 75 per cent of patients having acute glomerulonephritis [5, 6, 7, 11, 24] and are considered to indicate "myocardial damage" either functional or anatomical. There is no close correlation between the severity of the electrocardiographic changes and the degree of heart failure[ibid.] which might be expected if the failure were due to morphological changes in the myocardium. Various electrocardiographic changes have been described, such as isoelectric, negative, or high pointed T-waves and, more rarely, a deviation of the electrical axis to the left.

Four of our patients had tracings which were within normal limits. Five had minor changes consisting of transient lowering of the voltage of the T-waves in three patients and high, pointed T-waves in two patients. In three patients, the electrocardiogram showed left axis deviation and sharply

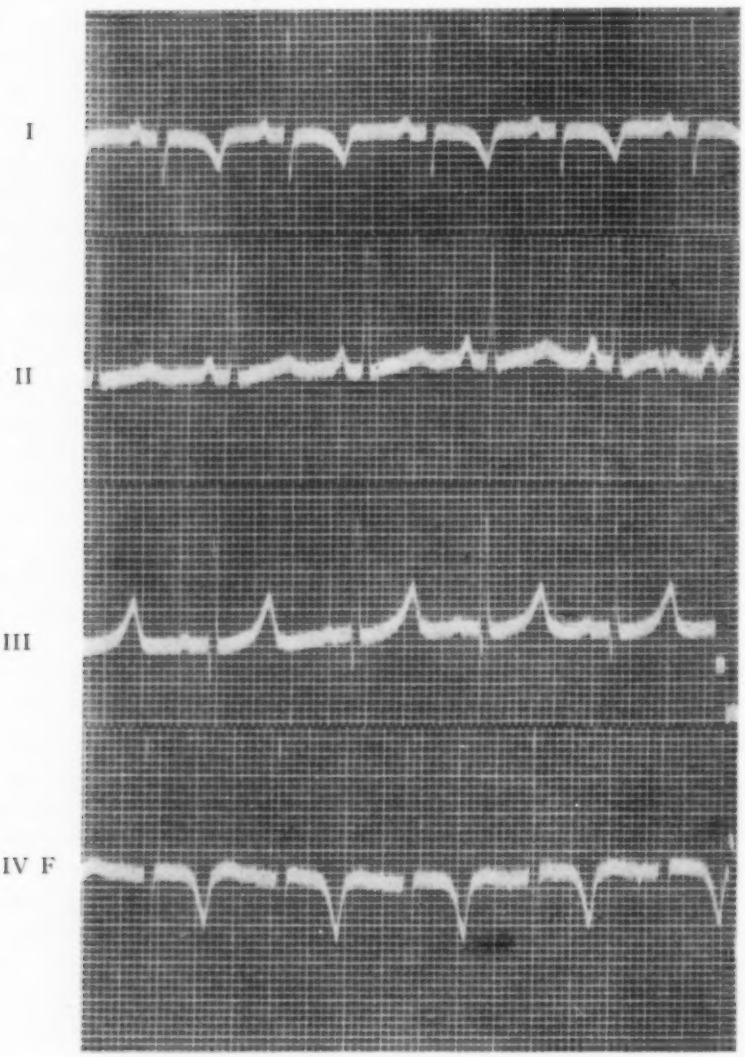

FIG. 3. Electrocardiogram of patient 4 showing sharply negative T_1 and T_4 on the 10th hospital day.

negative T-waves in Leads I and IV F (figure 3). These T-wave changes indicated that the myocardium of the left ventricle was acting as if it were ischemic.[25] In all but two patients, the electrocardiogram was normal at the time of discharge. The ventricular gradient in the electrocardiogram shown in figure 3 has undergone clockwise rotation which was noted in five other instances. The findings will be reported in detail later.

General legend for Charts 1 to 12.

These charts record the variations and changes in each patient's weight, blood pressure, venous pressure, circulation time, fluid intake and output, diastolic heart volume, degree of peripheral edema, albuminuria, hematuria, cylindruria and level of the blood urea nitrogen. The relationships of these changes are noted for each chart and are discussed in the text.

Key for abbreviations used in Charts 1 to 12.

S.B.P. —systolic blood pressure in mm. of mercury
D.B.P. —diastolic blood pressure in mm. of mercury
Wt. —weight in pounds
V.P. —venous pressure in cm. of water
C.T. —circulation time in seconds (prochalon, arm to tongue)
V.C. —vital capacity in cubic centimeters
D.H.V. —diastolic heart volume in cubic centimeters
Edema —peripheral leg, arm, or sacral edema graded 1 plus to 4 plus
Alb. —albuminuria graded 1 plus to 4 plus
R.B.C. —microscopic hematuria seen under high power in a centrifugalized specimen and described as occasional, few, many, or loaded
Casts —granular casts seen under high power field of centrifugalized urine and described as occasional, few, many, or loaded
B.U.N. —blood urea nitrogen in milligrams per 100 c.c. of blood

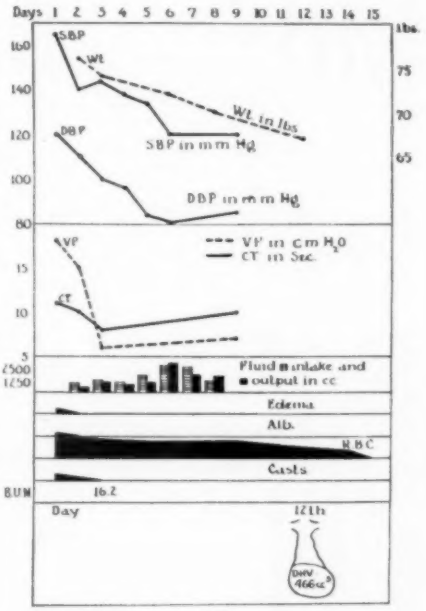

CHART 1. In this 11 year old colored boy an initial drop in the blood pressure preceded the fall in venous pressure and weight. The transverse diameter of the heart decreased 1.1 cm. in three days. The circulation time was always within normal limits.

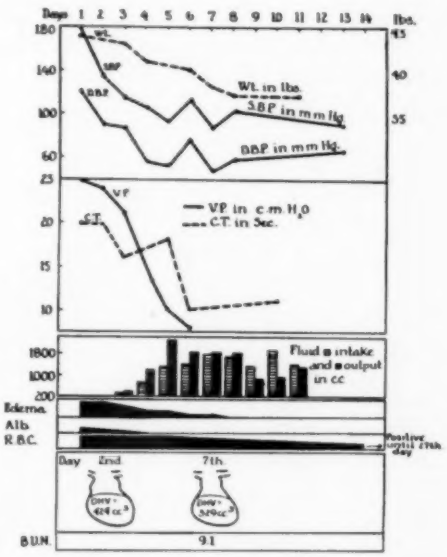

CHART 2. In this six year old colored girl the blood pressure fell before there was any great change in the weight or venous pressure. By the seventh day the diastolic heart volume had decreased 95 c.c. as indicated by the reduced tracings of the actual teleroentgenograms. This is the only patient who had an elevated circulation time. She was so sluggish mentally that it was difficult to be sure that the elevation was significant.

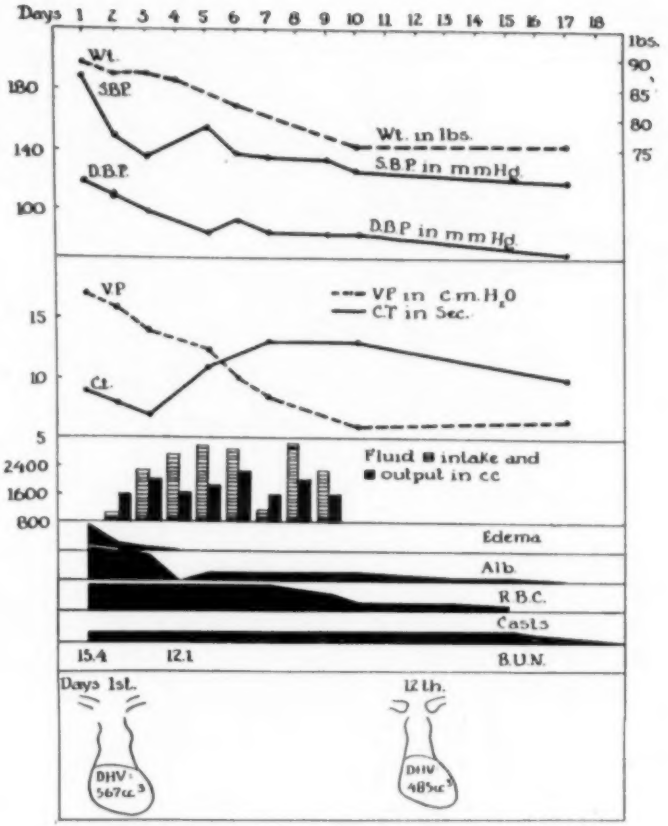

CHART 3. In this 12 year old white boy a significant fall in the blood pressure preceded the fall in venous pressure. By the 12th day the diastolic heart volume had decreased 82 c.c.

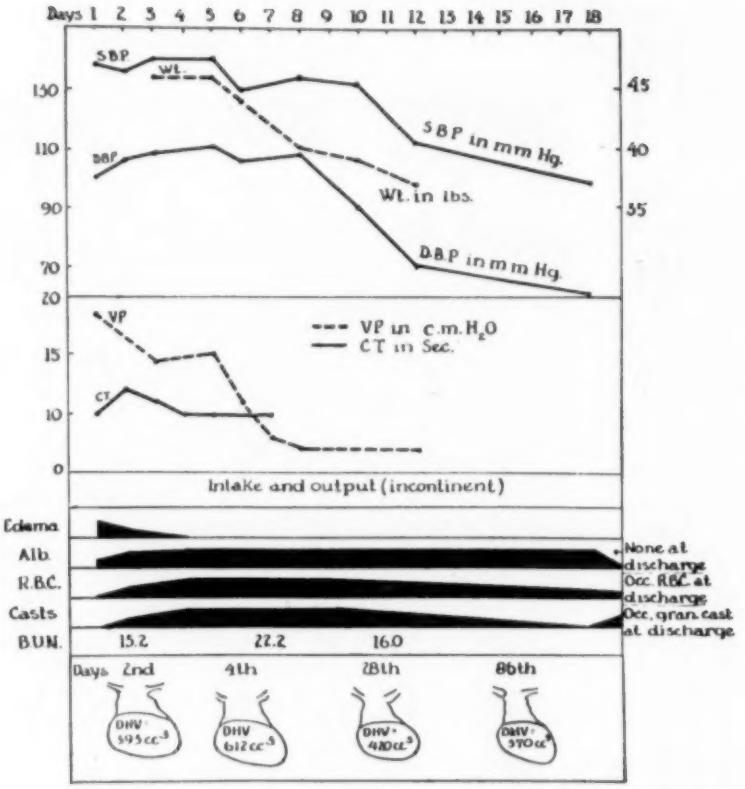

CHART 4. In this five year old colored boy the blood pressure failed to fall before the venous pressure. On the 28th day there had been a decrease in the diastolic heart volume of 192 c.c. and 86 days after admission to the hospital there had been a final decrease of 242 c.c.

day the diastolic heart volume had decreased 82 c.c.

decrease in the diastolic heart volume of 192 c.c. and 86 days after admission to the hospital there had been a final decrease of 242 c.c.

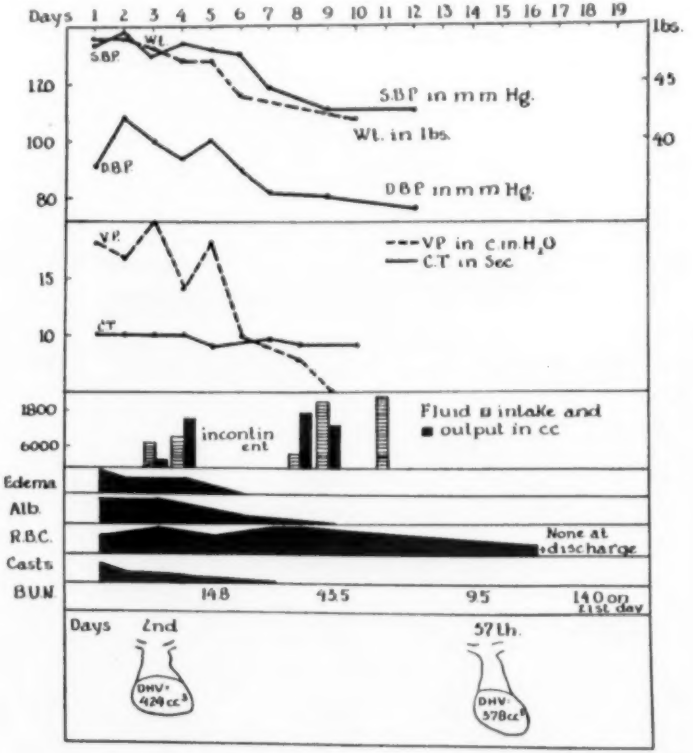

CHART 5. In this seven year old colored girl the blood pressure fell before the venous pressure had returned to normal. On the 37th day there had been a decrease of 35 c.c. in the diastolic heart volume and 1.4 cm. in the transverse diameter of the heart.

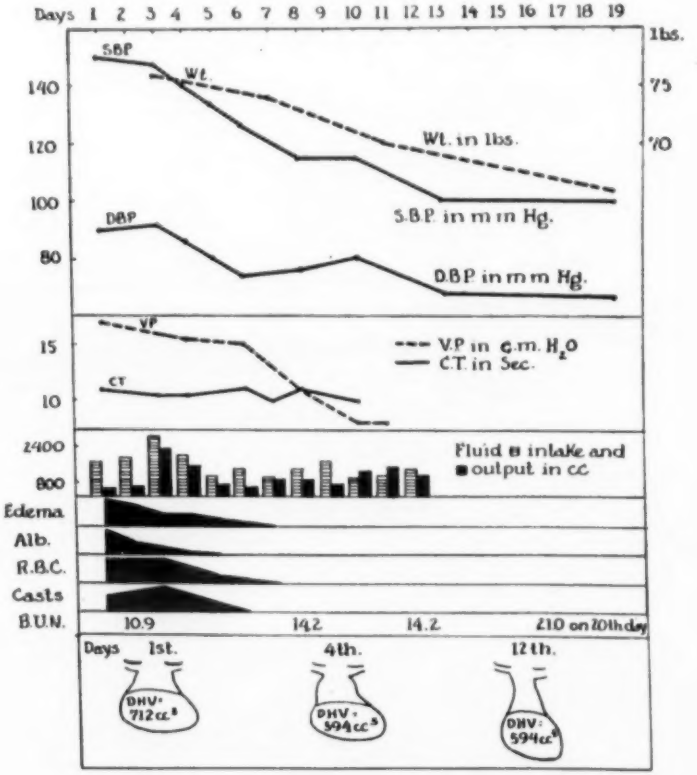

CHART 6. This 10 year old colored girl had a fall in blood pressure definitely preceding the return of the venous pressure to normal limits. On the fourth day the diastolic heart volume had decreased 118 c.c.

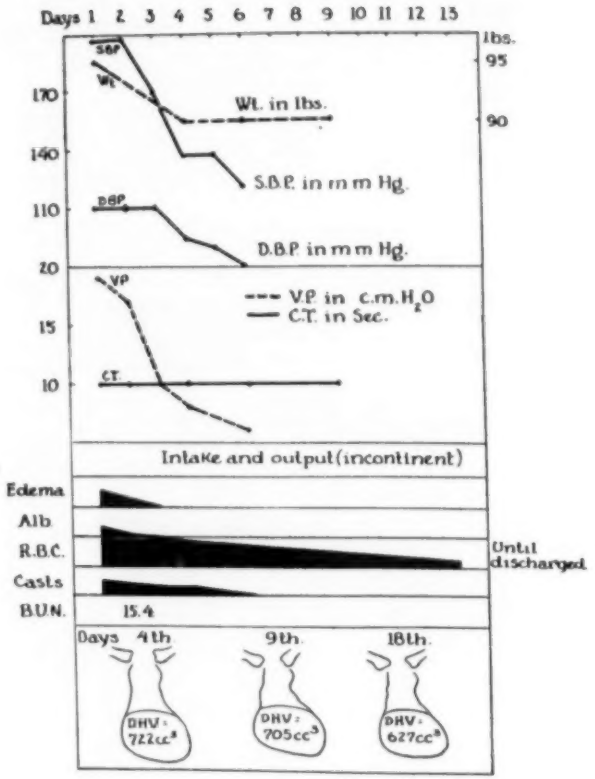

CHART 7. In this 13 year old white youth the fall in blood pressure and venous pressure appeared to be almost simultaneous. By the ninth day the diastolic heart volume had decreased 17 c.c. and by the 18th 85 c.c.

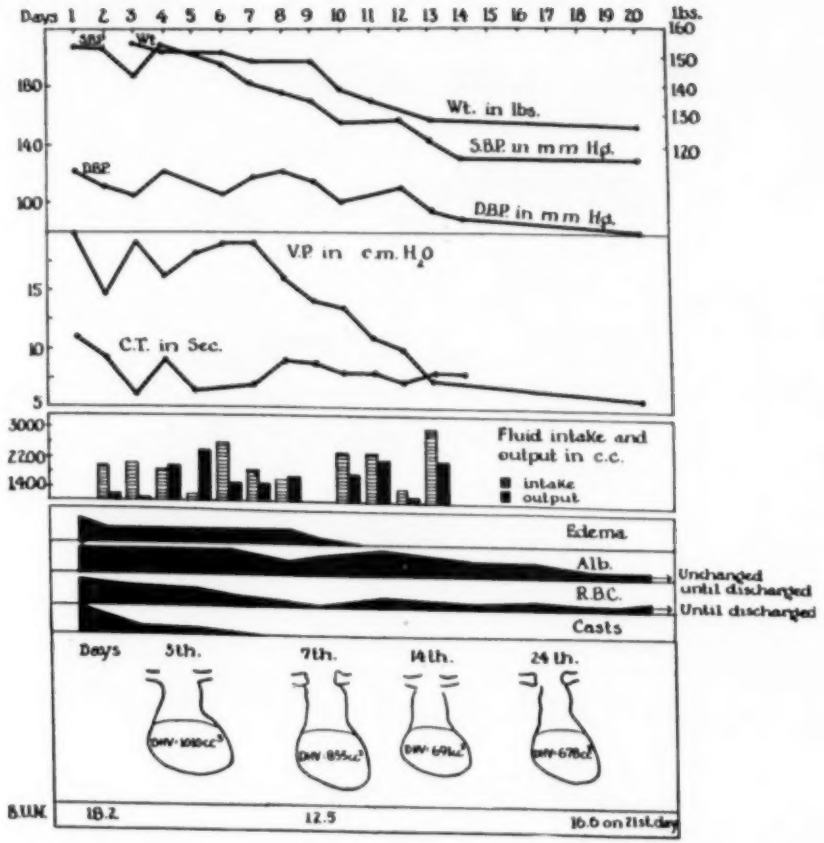

CHART 8. In this 16 year old colored boy the fall in blood pressure preceded the fall in venous pressure. On the seventh day a decrease of 155 c.c. in the diastolic heart volume was noted; on the 14th day the decrease was 319 c.c.; and on the 24th day 332 c.c.

had decreased 17 c.c. and by the 18th 85 c.c.

and on the 24th day 332 c.c.

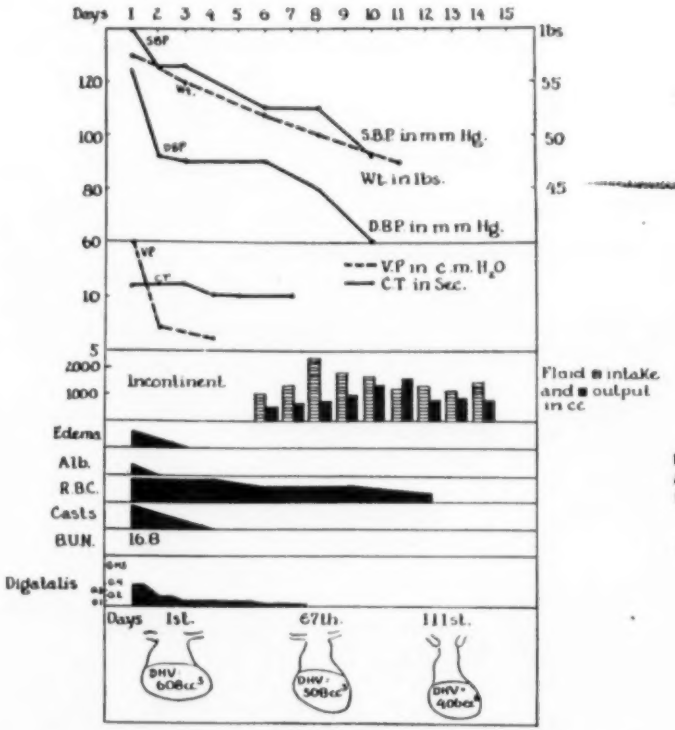

CHART 9. This eight year old colored boy received digitalis as indicated. His venous pressure fell to normal within 24 hours but the blood pressure remained elevated for nine days. The diastolic heart volume on the 67th day was 100 c.c. less than on admission.

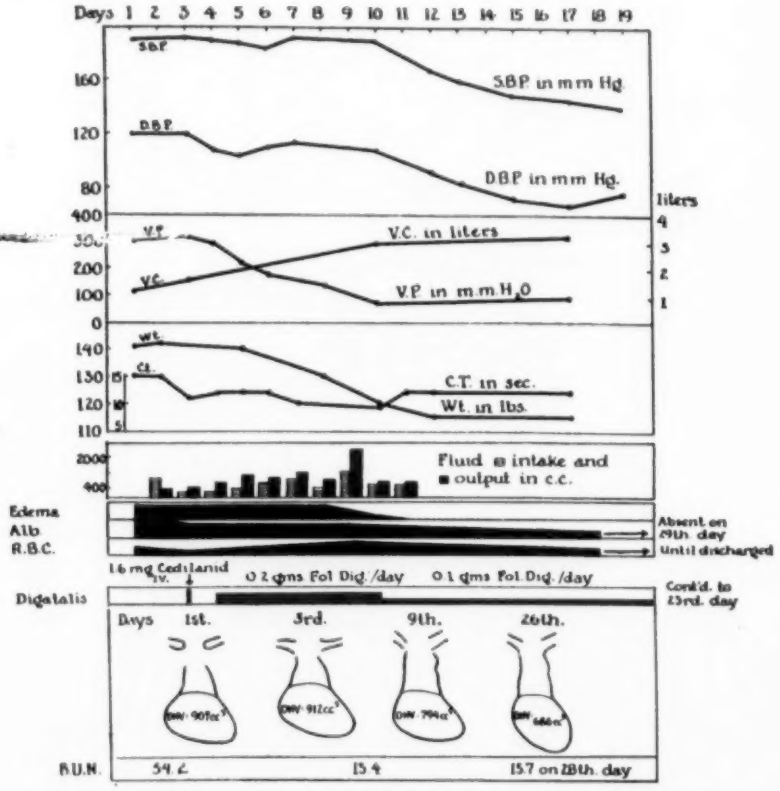

CHART 10. This 16 year old colored male was given Cedilanid intravenously. His venous pressure and vital capacity were within normal limits long before any fall in blood pressure occurred. On the ninth day the diastolic heart volume was 118 c.c. less than on admission and on the 26th day it was 226 c.c. less.

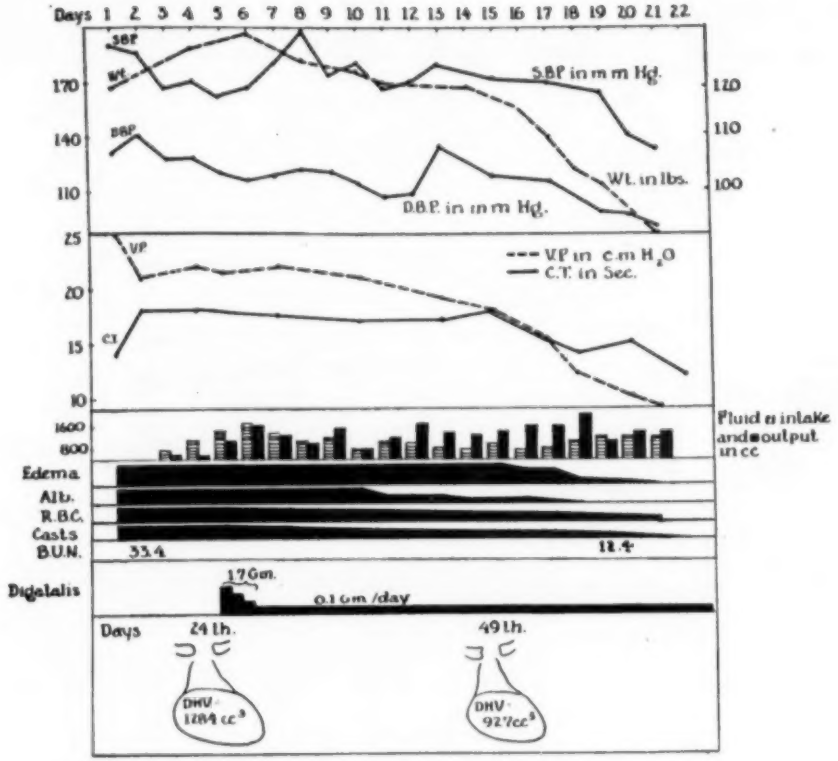

CHART 11. This 25 year old colored woman with acute glomerulonephritis developed increasingly severe congestive heart failure until she was digitalized. The fall in venous pressure slightly preceded that in blood pressure. Because of pleural effusions, the diastolic heart volume could not be determined early, but between the 24th and 49th days a decrease of 357 c.c. occurred.

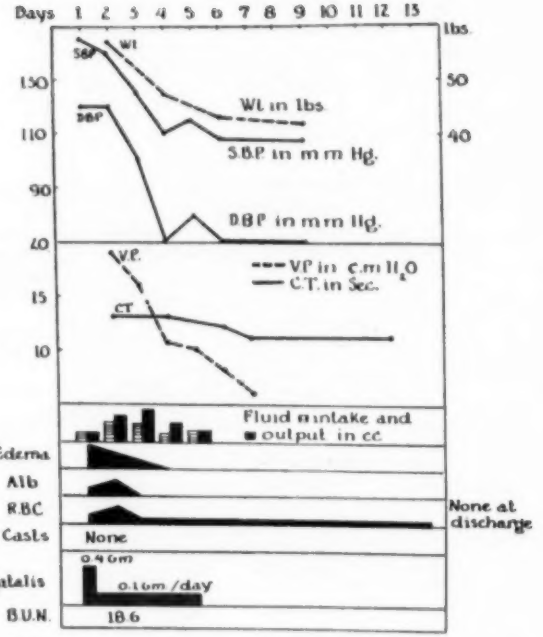

CHART 12. This nine year old colored boy with mitral stenosis and acute glomerulonephritis was given digitalis. The blood pressure and venous pressure appeared to fall simultaneously. The transverse diameter of the heart was 1 cm. less on the fourth day than on admission.

Conclusions

1. The edema of 12 patients with acute glomerulonephritis was found to be associated with right heart failure as indicated, in every instance, by an elevated venous pressure and cardiac dilatation.

2. In nine patients most of the symptoms of congestive heart failure were present, but in three patients the presence of peripheral edema was the only symptom suggesting heart failure. More careful study of these three patients disclosed cardiac dilatation and elevated venous pressure.

3. The importance of hypertension in the pathogenesis of and relief of the congestive heart failure which frequently complicates acute glomerulonephritis has been emphasized. The earliest objective evidence of improvement of the heart failure in seven of eight patients not given digitalis was a fall in blood pressure; the return to normal of the venous pressure and the disappearance of edema occurred slightly later.

4. There was a significant decrease in the diastolic heart volume of these patients after compensation had been established. This decrease was even greater two to four weeks after congestive failure had disappeared.

5. The circulation time was normal or low in 11 of 12 patients studied, despite an elevation of the venous pressure.

6. The pulmonic second heart sound was accentuated in 11 of 12 patients, suggesting the possibility of pulmonary hypertension.

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MULTIPLE PERIPHERAL NEURITIS OCCURRING WITH SULFONAMIDE THERAPY *

By M. A. BLANKENHORN, F.A.C.P., *Cincinnati, Ohio*

MULTIPLE peripheral neuritis occurring with sulfonamide therapy may become an important consideration as such therapy is extended and as the drugs are used prolongedly in infections. The incidence of such neuritis at present is difficult to ascertain. Only isolated cases are reported. It is said that the complication is rare and that it may follow prolonged use and large dosage.[1]

During the treatment of approximately 627 patients on the medical service of the Cincinnati General Hospital in 1942, peripheral neuritis occurred in six instances in which sulfonamides must be considered as a possible cause.

Multiple peripheral neuritis is not a rare disease at the Cincinnati General Hospital, but the cause of it is often a matter of inference rather than proof. In the past five years multiple peripheral neuritis has been the diagnosis 105 times among 12,200 admissions to the medical service, an incidence of .85 per cent. It is probably true that the apparent incidence of neuritis at the Cincinnati General Hospital is enhanced by the inclusion of mild types, because of the more careful examining of our physicians. The incidence of all deficiency diseases among the medical admissions has been reported as "about 2 per cent." [2]

Our incidence of neuritis after sulfonamides is about 1 per cent. What effect susceptibility to neuritis has on this incidence of neuritis after sulfonamides would be worth knowing and perhaps helpful in preventing drug neuritis.

These patients diagnosed as having multiple neuritis are of two sorts by clinical description and of five classes as to suspected cause. Clinical types may be classed simply into the paralyzed and the non-paralyzed. Forty of 105 cases were paralyzed, i.e., had marked weakness causing wrist drop, foot drop or both. The non-paralyzed had less obvious signs and probably represent a milder degree of neuritis, possibly a different kind. Aring [3] on a number of occasions has described this milder condition as typical American beriberi. It is prevalent among the pellagrins in our Nutrition Clinic at Birmingham, Alabama,[4] and it responds to certain therapy in a manner that can hardly be fortuitous. It is his opinion, and our experience at the Cincinnati General Hospital, that nutritional neuritis (i.e., beriberi) rarely causes paralysis.

* Read at the regional meeting of the American College of Physicians, Columbus, Ohio, May 14, 1943.

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Beriberi Neuritis

The neuritis associated with pellagra is recognized by the complaints of pains in the calf muscles and of weakness, numbness and tingling of the extremities. The physical signs are those of tenderness to deep pressure, exaggeration or reduction of tendon reflexes, change in several sensory modalities both as hyperesthesia and hypoesthesia. Striking signs, not often simulated, are delay in perception of pinprick, and of "afterglow," that is, persistence of sensation, on stroking with an applicator. This type of pure nutritional neuritis is rapidly improved by thiamine or brewers' yeast, but if untreated it rarely goes on to paralysis.

Biopsy of a small nerve trunk from a chronic pellagrin with this form of neuritis usually shows quantitative reduction in the number of myelinated fibers in a transverse section of nerve. It may be noted that patients suffering from chronic, recurrent pellagra, who have no complaint and no physical sign of neuritis, also may have reduction in the number of nerve fibers.

It is Aring's opinion [5] that paralyzing neuritis seldom occurs except in patients whose nutritional deficiency is associated with alcoholism, or in those who have severe disease of other than nutritional origin. It was his observation that when pellagra and alcoholism were combined the myelin fiber counts were lowest, and paralysis was present.

It may be seen in the case material to be discussed that when several possible etiologic factors are present, the effects of sulfonamide may be paralyzing. It cannot be claimed that sulfonamide is the sole cause of neuritis in any instance here described.

Clinical Classification of Neuritis

The 105 patients with neuritis who have been examined at the Cincinnati General Hospital may be divided into five groups according to suspected association, viz., diabetes, alcoholism, infections, unknown or nutritional causes and drugs.

Of 17 diabetics, 1 was paralyzed	6%
Of 27 unknown (nutritional?), 9 were paralyzed	33%
Of 34 alcoholic, 15 were paralyzed	44%
Of 19 infectious, 12 were paralyzed	63%
Of 6 sulfonamide, 3 were paralyzed	50%
Of 2 arsenic, 0 were paralyzed	0%

In fairness to this attempt at etiological diagnosis, it should be said that severity is not used as a criterion of causes. The history and the presence of associated disease mainly decide the issue.

Case Material

Table 1 records the details of case material, here presented as neuritis possibly caused by sulfonamide treatment. In each instance there was multiple peripheral neuritis with onset in hospital during the administration of the

TABLE I

Peripheral Neuritis after Sulfonamide Treatment

Case No.	Age	Sex	Race	Hosp. Days	Result	Paralyzed	Onset	Principal Diagnosis	Total Drug	Blood Level	Alc.	Diet	Obvious Defic.	Other Treatment
1	40	M	B	63	Well	Yes	Abr.	Mg. meningitis	Diaz. 89	15			Edema decubitus	Iv, Glucose, serum
2	44	F	W	42	Well	No	Slow	Lobar pn. types 7 and 18 Chr. pul. disease?	Thiaz. 52	12				Iv, Glucose, serum
3	27	M	W	21	Well	No	Abr.	Pn. 3, Meningitis Pn. 3, Bacteremia	Diaz. 68	15		Good		Iv, Glucose, serum
4	37	M	B	56	Well	No	Slow	Pn. 5, Pneumococcal pyarthrosis Pn. 5, Bacteremia	Pyraz. 37 Thiaz. 160	13 3.8	Yes	Good		Iv, Glucose, serum
5	45	M	W	70	Well	Yes	Abr.	Bronchopneu.	Diaz. 24 Thiaz. 42	5 3.6	Yes	Poor	Cirrhosis	Iv, Glucose, B_1 before drug
6	26	M	B	35	Imp.	Yes	Abr.	Pneumonia Pn. 4	Thiaz. 36	5.1	Yes	Poor	Neuritis 10 mo. before cleared promptly with B_1	None

drug in question or in the convalescence. There was no fever nor cerebrospinal fluid changes referable to neuritis alone. In all instances the drug was given by mouth, a gram every four hours. Intravenous doses were few and are indicated in footnotes. Other treatment, such as serum administration, is indicated because of its etiologic possibility. Glucose is mentioned because five out of the six cases received glucose, occasionally in large amounts. Three patients showed occasional glycosuria, but there was no case with excessive blood sugar or high blood urea.

The use of intravenous glucose is mentioned, also, because I am impressed by the frequency with which acute glossitis and mental symptoms such as those associated with niacin deficiency, as well as mild symptoms of neuritis, may occur after the prolonged use of glucose intravenously. It is becoming a custom to give the patients in this condition polyvitamin therapy if they cannot take a proper diet. Just as I do not know the cause of neuritis in a diabetic, I do not know the relation of this use of glucose to neuritis.

In table 1 it is indicated that four of six patients were treated with antiserum. None had serum sickness. None of these patients had severe pain at the onset such as is common in the type of neuritis seen after serum treatment. The serum given for pneumococcal disease was rabbit serum and that for meningococcal meningitis was antitoxin, not antiserum.

Serum and Neuritis

The rôle of any serum in causing neuritis is not known. We have given horse and rabbit serum to 445 patients with lobar pneumonia and caused serum sickness in about 15 per cent when horse serum was mainly used. We have not caused neuritis by serum when serum alone was used. Neuritis after antiserum, as described by Wilson and Hadden [6] and by Young,[7] is usually associated with serum sickness, has a latent period of onset, involves the upper extremities and is painful as well as paralyzing. In 50 collected cases of neuritis following serum treatment, Young found three examples of polyneuritis such as is described here with sulfonamides.

In a paper of this scope it is useless to say more than that neuritis is rare in untreated pneumococcal pneumonia and that the rôle of the pneumococcus is unknown in the neuritis here described.

None of our patients with neuritis associated with sulfonamides showed any other evidence of drug intoxication. Only one had received a similar drug at any previous time, and that was a year before.

Alcohol and Neuritis

The rôle of chronic alcoholism in the production of neuritis that follows sulfonamide therapy is just as much a mystery as the relation of alcohol to neuritis, otherwise uncomplicated. In our cases chronic alcoholism was certain in three and suspected in a fourth. Three cases gave a history of poor diet and showed evidence of deficiency disease.

Aring [8] finds the "concept of nutritional deficiency neuritis which has come to the fore within the last decade not as clear and final as those who advocate vitamins as a panacea would lead one to believe." We are even less clear about alcohol and neuritis and cloudier still about the combination of vitamin deficiency, alcohol and sulfonamides. We think that chronic alcoholics may go about with nerve trunks which have a reduction in the number of their nerve fibrils; and there can be no doubt that alcoholic addiction and peripheral neuritis may be related. Further interpretation seems unwarranted when our material is examined critically.

We believe that paralyzing neuritis due to alcohol or to anything else is not much improved by vitamins. In two instances (Cases 6 and 12) neuritis in an upper extremity became better, whereas that in the lowers became worse. Regional factors perhaps related to the blood vessels of the nerves may be a factor in such uneven distribution.

Case 5

Initial dose of sulfadiazine was 4 gm. intravenously.
Sulfathiazole was given after a short free interval. Highest blood urea nitrogen was 21 mg. per cent.
Glucose as 5 per cent solution parenterally totalled 675 gm.
Onset of neuritis was abrupt after 28 days of intense vitamin therapy, viz.:

Thiamine	50 mg. inj. daily × 28 days.
Niacin	300 mg. inj. daily × 23 days.
Liver extract	2 c.c. inj. daily × 6 days.
Brewers' yeast	6 oz. inj. daily × 3 days.

Case 6

Sulfathiazole started 10/1/42.
Neuritis onset 10/10/42.
Vitamin therapy started 10/10/42, as follows, daily for 18 days:

Thiamine inj.	25 mg.
Thiamine by mouth	15 mg.
Niacin by mouth	150 mg.
Yeast by mouth	1.5 oz.

Fifty milligram and 25 milligram doses were injected intravenously; 10 mg. and 5 mg. occasionally were injected hypodermically.
After 18 days polyneuritis much improved though worse in right lower extremity (foot drop).

Treatment

Table 1 shows five patients were discharged as "well" and the sixth as "improved." No. 6 continued to improve with physical therapy but in the seventh month of convalescence had mild residual weakness.

We believe that mild neuritis may not be cured by thiamine alone and, therefore, usually give niacin, riboflavin and yeast as well, whenever neuritis is being treated energetically. In the tables shown, only thiamine is indicated; the dose was from 10 to 50 mg. by daily injection. Other vitamins were not consistently given and, therefore, were not charted. They were given in large amounts together with a rich diet whenever possible. Exceptions are shown in footnotes.

Table 2 shows case summary of eight patients known to have signs of deficiency diseases including neuritis before any sulfonamide was given.

TABLE II

Peripheral Neuritis before Sulfonamide Treatment

Case No.	Age	Sex	Race	Hosp. Days	Result	Para-lyzed	Onset	Principal Diagnosis	Total Drug	Blood Level	Alc.	Diet	Obvious Defic.	Other Treatment
Unchanged by Sulfonamide Treatment														
7	62	M	B	77	Well	No	Slow	Bronchopneu.	Diaz. 42	9	Yes	Poor	Glossitis	lv, Glucose, serum B_1, Before drug
8	56	M	W	42	Well	No	Slow	Lobar pneu. Pn. 3	Thiaz. 24 Diaz. 42	6 5	Yes	Poor	Cirrhosis, neuritis on adm.	lv, Glucose, serum B_1, Yeast before drug
9	75	M	W	17	Well	No	Slow	Cong. failure	Diaz. 16			Poor	Pellagra, neuritis? Ariboflav.	lv, Glucose, digitalis
10	80	M	W	35	Well	No	Slow	Bronchopneu. Gastric bleeding	Thiaz. 14	3.0		Good	Anemia, neuritis?	B_1, Before drug
11	40	F	B	21	Well	No	Slow	Acute bronchitis	Diaz. 15			Poor	Edema, pell., anemia	B_1, Before drug
Made Worse by Sulfonamide Treatment														
12	59	M	W	31	Well	Yes	Slow	Lobar pneu. bacteremia Pn. 20	Thiaz. 30	2	Yes	Poor	Neuritis before drug, cirrhosis?	lv, Glucose B_1, During drug
Better During Sulfonamide Treatment														
13	46	M	W	21	Well	No	Slow	Pneumonia Pn. 4	Thiaz. 17	17	Yes	Poor	Neuritis on adm.? Cirrhosis	B_1, During drug
14	38	M	W	49	Well	No	Slow	Diabetes	Thiaz. 34 Diaz. 15	3.7	?	Poor	Sprue?	None

These should all be regarded as showing the American type of beriberi. Only one (No. 8) received more than 50 gm. of drug and a few had quite small doses. All had gross evidence of deficiency and all except one had history of poor diet.

Six of the eight were treated with vitamins (injections of thiamine) or yeast before or during the administration of sulfonamides. This group did not receive large doses of glucose by vein, although four were so treated. It is possible that severe neuritis was prevented by proper supportive treatment.

Case 7

Vitamin therapy was started on admission as follows:

Thiamine	50 mg. inj. daily × 10 days.
Niacin	100 mg. inj. daily × 20 days.
Thiamine	10 mg. inj. daily × 10 days.

Case 8

Vitamin therapy was started on admission as follows:

Thiamine	20 mg. inj. daily × 5 days.
Niacin	200 mg. inj.
Liver extract	3 c.c. U.S.P. inj. daily × 6 days.

Case 9

Niacin	400 mg. daily × 4 days before any sulfonamide.
Thiamine	50 mg. daily after second day of sulfonamide.

Case 10

Niacin	100 mg. daily.
Thiamine	10 mg. daily.

Started before sulfonamide.

Case 11

Vitamin therapy was started on admission as follows:

Thiamine	50 mg. inj. twice daily × 7 days.
Liver extract	50 U.S.P. units inj. daily × 6 days.

Case 12

Neuritis in uppers became better, and in lowers became worse. Vitamin therapy was started on admission, which was three days before sulfonamide therapy:

Thiamine	50 mg. inj. daily × 9 days.
Niacin	50 mg. inj. daily × 5 days.

Case 13

Vitamin therapy was started the day after sulfonamide therapy:

Thiamine	5 mg. twice daily by mouth.

Summary

Six cases of multiple peripheral neuritis occurred among the 600 treated with sulfonamide drugs. In five instances the total dose was 50 grams or more; 6 grams per day were administered by mouth. The largest dose was 197 grams and the smallest was 36 grams. Blood levels of the drugs were not unusual.

In several cases other factors, mainly alcoholism or deficiency states, may have contributed.

Eight cases are reported showing signs of neuritis before sulfonamide drugs were given. Of these patients with mild neuritis, only one was made worse by sulfonamide treatment.

Vigorous treatment with vitamins and diet may have prevented the neuritis from becoming worse.

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WHY PLASMA *

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Experience with the University Blood and Plasma Bank has led me to believe that a discussion of the indication for plasma is apropos. There is a tendency today to substitute plasma for whole blood when blood would be more appropriate. This tendency is based usually on the greater ease of plasma administration rather than on careful consideration of indications for plasma. It should be pointed out that blood storage has reached the stage where by the use of a preserving solution whole blood can be kept for 21 to 30 days. This makes blood readily available and shortens materially the time required for securing blood in an emergency.

Plasma, however, does represent a real contribution to the armamentarium of the physician, and it is essential that he be familiar with its indications and contraindications. Plasma may be secured as a by-product of blood banking, or it may be secured from fresh blood by centrifugation or sedimentation.

The first step in the preparation of plasma obviously consists of the collection of the blood, and for this purpose an anticoagulant must be used. Some of the more common solutions advocated are given in the table. Simple citrate is recommended if the blood is to be used at once for the preparation of plasma, whereas the dextrose citrate buffer solution has been found extremely satisfactory for the preservation of blood, which can be converted into plasma at the end of 21 to 30 days, if it has not been used as whole blood in the interim. This method also lends itself well to the sedimentation technic, giving a plasma which has been diluted and thus obviating a step which is recommended by some workers [7] who suggest dilution of the normal plasma with saline and glucose if it is to be stored. The second step in the production of plasma is the separation of the cells from the plasma. This can be done either by sedimentation or centrifugation. The yield of plasma from undiluted blood is increased by centrifugation. This is a laborious step necessitating the use of cold blood, cold centrifuge cups, etc., to avoid hemolysis which develops if the blood "heats up" during centrifugation. Hill [8] and his co-workers recommend the use of a separator much like a cream separator. Once the separation has been accomplished, regardless of the method, the next step is the removal of the plasma into a pooling flask, usually by aspiration. For clinical purposes a pool of eight to 10 assorted bloods is satisfactory. The pool should be allowed to stand for 24 to 48 hours, at which time it may be tested for the titer of the isoagglutinins and if they are found to be too high, e.g., above 1–20, appropriate

* Read before the Regional Meeting of The American College of Physicians, Kansas City, Mo., May 8, 1943.

TABLE I

Solutions Used for Blood Banking

Name	Composition		Solution	Blood
			c.c.	*c.c.*
Moscow Institute of Hematology[1, 1a]	Sodium chloride	8.0 gm.	100	100
	Sodium citrate	5.0		
	Potassium chlor.	0.2		
	Magnesium sulf.	0.4		
	Distilled water	1,000.0		
Strumia and McGraw[2]	Sodium citrate	40.0	10	100
	Sodium chloride	8.5		
	Distilled water	1,000.0		
Patton[3]	Sodium citrate	25.0	70	430
	Distilled water	1,000.0		
Cook County Hospital	Sodium citrate	25.0	14	100
	Sodium chloride	8.5		
	Distilled water	1,000.0		
De Gowin et al.[4]	*Sol. I*		13	10
	Dextrose anhy.	5.4		
	Distilled water	100.0		
	Sol. II		2	
	Dihydric sodium citrate	3.2		
	Distilled water	100.0		
Gwynn and Alsever[5]	*Sol. I*		50	400
	Dextrose	20.0		
	Distilled water	100.0		
	Sol. II		50	
	Sodium citrate	5.0		
	Sodium chloride	4.6		
	Distilled water	500.0		
Muether and Andrews[6]	Dextrose	46.8	150	100
	Sodium citrate	4.3		
	Monobasic sodium phos.	.25		
	Dibasic sodium phos.	2.5		
	Distilled water	1,000.0		

plasma of one type or another should be added. Our experience has shown that most pooled plasma will have an agglutinin titer of 1 : 20 or less. The pool should be cultured aerobically and anaerobically and tested for toxicity. This is the fourth step in the preparation of plasma. When the pool has been shown to be satisfactory, it is aspirated into dispensing units for final disposition. Plasma can be kept in three forms, liquid, frozen, or dried. Liquid plasma may be stored at room temperature or it may be kept in a refrigeratory at 5 to 8° C. The advantages of room temperature storage are: (1) that it does away with the need for refrigeration, and (2) precipitate forms more slowly. The disadvantages of such storage are the rapid loss of complement and prothrombin and the dangers of contamination. Liquid plasma kept at refrigeration temperature quickly develops a precipitate

but tends to lose its prothrombin and complement more slowly, and the growth of bacteria is also inhibited somewhat. There is, however, no real difference between these two kinds of plasma since prothrombin and complement are very seldom important, and the presence of bacteria, regardless of how few, means that the plasma is unsatisfactory and must be discarded. The use of the various bacteriostatic agents that have been advocated should probably be condemned since they tend to give a false sense of security and may cause minor errors or breaks in technic to be ignored on the supposition that the bacteriostatic agent will take care of the error. Sulfanilamide seems particularly undesirable since the use of large quantities of plasma containing this drug might well lead to the development of untoward side effects.

The protein content of the plasma should be determined and should be recorded on the tag of each bottle so that the plasma can be administered on the basis of protein content rather than volume.

Frozen plasma retains its complement and prothrombin titer well and when thawed does not have much if any precipitate. This does not mean, however, that the plasma should be administered without a filter. All plasma as well as blood is best given through a filter. The stainless steel type of about 100 mesh has proved very satisfactory.

Frozen plasma requires special equipment for initial freezing, particularly if it is to be "shell frozen," and it must be stored in a special refrigeratory capable of maintaining a temperature well below 0° C. Frozen plasma requires considerable time to thaw and should be thawed at a temperature of 38° C. This usually takes 30 minutes or more. Freezing then is best suited to the long storage of large quantities of plasma intended to be used as a supplement to the more readily available types of plasma.

Dried plasma keeps well at any temperature and can be stored indefinitely. It retains complement and prothrombin well, and is rapidly restored to the liquid state on the addition of water. Strumia has suggested that the prothrombin and complement may be lost on reconstitution with plain water because of change in pH. It can be reconstituted in one-fourth or one-fifth of the volume of liquid originally removed and thus a hypertonic solution can be developed suitable for the treatment of certain selected conditions. The disadvantage of dried plasma is the increased cost of production and the need for special equipment and personnel. As will be noted in the table the plasma can be dried in any one of a variety of ways all of which have worked well in the hands of the originators. Dried plasma is particularly suitable for transportation over great distances because of the decreased weight which results when the fluid is removed.

The Use of Plasma: If we exclude the use of plasma for its antibody properties we can look upon it as a physiological protein solution. The indications for its use can be divided roughly into three large classes, namely: (1) hemoconcentration, (2) hypoproteinemia, (3) anhydremia and dehydration.

Hemoconcentration: Much has been written concerning hemoconcentration, but there is no general agreement as to just what factors are involved in its production. It is quite evident that hemoconcentration is no simple phenomenon; it involves water and electrolyte balance as well as altered vasomotor reactions, etc.[9] The diagnosis of hemoconcentration is almost always predicated on an initial normal intravascular volume since it is very difficult if not impossible to determine exactly what the actual status was before the emergency arose.[10] The hematocrit is one of the simplest means of determining whether or not hemoconcentration is taking place. The total plasma protein may be helpful in this connection, but it should be emphasized that hemoconcentration may occur without an increase in the total protein. The protein may actually fall if capillary permeability increases and permits the loss of large quantities of protein into the tissues. The use of the falling drop technic [11, 12] for the determination of the specific gravity is helpful and very rapid. The determination may be done on whole blood, plasma, or serum. Other changes in blood may be noted during the course of hemoconcentration such as increase in plasma potassium,[13] but these changes are less helpful than some of the simpler procedures. Once the diagnosis is made it is essential that treatment be rapid and proper. The restoration of the blood volume is of paramount importance and all other procedures are secondary as a rule. It is immediately necessary, therefore, to determine how much plasma is necessary for this restoration, and several formulae [14, 15] have been devised to aid in these calculations. Harkins [10] suggests using a simple method, namely, giving 100 c.c. of plasma for every point above a hematocrit reading of 45. This is, I believe, too small an amount in most cases of shock, but is a rough indication of the initial dose to be given; as the plasma is administered the hematocrit can be repeated, more plasma being given if necessary to return the hematocrit to normal. Most physicians tend to give too little rather than too much plasma. The plasma may be administered continuously or it can be given at intervals. The plasma may be given satisfactorily by sternal puncture as recommended by Tocantins and co-workers.[16] The use of the dilute plasma, that is, plasma which contains about 3 grams of protein per 100 c.c., has been simple and entirely satisfactory in our experience. The use of normal plasma is of course extremely satisfactory. Concentrated plasma has been advocated by some on the basis that its hypertonic effect will draw tissue fluid into the blood stream. The concentrated plasma should be used cautiously, however, since the altered permeability of damaged capillary and the local loss of fluid which takes place in shock tend to make it unlikely that a marked increase in intravascular osmotic pressure will pull fluid out of the injured area. It is much more likely that fluids from the normal tissues will enter the vascular tree and produce tissue dehydration which in turn will aggravate the general collapse. Our experience leads us to believe that fluid loss into the tissues is relatively unimportant if one can maintain a satisfactory intravascular volume thus as-

suring an adequate return of blood to the heart which in turn allows satisfactory oxygenation, etc., breaking the vicious cycle which develops in shock regardless of the cause.

Hypoproteinemia: Plasma is obviously extremely useful in this condition. The plasma bank has done a great deal to make available the large quantities which are necessary. It is possible to maintain a patient in nitrogen balance by the exclusive use of plasma as a source of nitrogen.[17] This is true even if heterologous plasma is used. Our experience with bovine plasma showed this, and other investigators have had similar experiences. The use of heterologous plasma, however, is not feasible because of the dangers of anaphylaxis associated with the prolonged or sporadic use of such plasma. We must confine ourselves at the moment to the use of human plasma, if plasma is to be used. The dose of plasma administered can be calculated so as to give the patient one to one and a half grams of protein per kilogram of body weight. The single administration of plasma in this way produces a temporary rise in the plasma proteins which does not persist. It usually is necessary to give numerous transfusions over a considerable period before a definite and persistent rise in the protein content of the blood occurs. If protein is being lost in considerable quantities in the urine, as in nephrosis, or by some other route, as may occur when large abscesses or sinuses are present, the protein loss must be estimated and the administered protein increased accordingly. This fact is frequently overlooked and the patient consequently inadequately treated.

Anhydremia and Dehydration: The sudden loss of blood volume, as in severe external hemorrhage, may lead to a crisis which can most readily be met by the administration of plasma. Whole blood is, of course, the ideal material, but if it is not available, plasma may be life saving. If the blood loss is 50 per cent of the total blood of the patient, however, plasma will not be sufficient and the initial administration of plasma must be followed by the administration of whole blood. The use of plasma in the treatment of dehydration is not necessary since simpler solutions will prove very satisfactory. However, in very marked cases, as for example those resulting from cholera, dysentery, or prolonged starvation, plasma may be very useful.

Reactions from Plasma: There has sprung up, on what basis is not clear, an idea that reactions do not occur when plasma is administered; this is not true [18] and no one who has had much experience with plasma can subscribe to it. It is true that the use of pooled plasma tends to eliminate reactions due to incompatibility, but even this is only relative since such reactions have been reported. Other types of reactions occur from the administration of plasma and must be kept in mind. Transfusion reactions in general can be divided into three types: (1) Those due to incompatibility which are usually hemolytic; (2) allergic reactions, which may manifest themselves as severe shock, or as milder forms such as urticaria, asthma, edema and the like; (3) pyrogenic reactions which may result from the use

of impure chemicals, improperly cleansed apparatus, incipient coagulative changes, etc. All of these reactions may occur when plasma or blood is administered. To avoid these reactions, it is wise to test the plasma for pyrogens and other toxic agents as well as to determine the titer of the iso-agglutinins present after pooling.

There is one other type of reaction which may be seen, which should probably be considered as mechanical. This reaction may occur from the administration of an excessive amount of fluid with an overloading of the vascular tree, resulting in acute cardiac failure with pulmonary edema. This reaction is more likely to occur in the elderly, the cardiac, or in persons with renal failure. The development of such a reaction is an indication for an immediate venesection as well as the prompt institution of supportive measures.

Conclusion: The answer to the question "Why Plasma?" is not the answer which is so often given, "Why Not?" Plasma is a very useful physiological solution which can be made constantly available at a reasonable cost in time, effort, and expense. It has definite limitations and should not be used when other substances, particularly whole blood, can be used to better advantage. Plasma transfusions are not without danger and may result in the same type of reactions as are associated with other transfusions. Reactions of incompatibility are unusual but apparently they may occur. Finally it should be pointed out that the ideal method for the procurement of plasma is as a by product of blood storage, that methods are available which permit the storage of blood for long periods of time, and that at the end of this storage period a satisfactory yield of plasma can be obtained. The type of plasma to be used in any institution depends entirely upon the facilities available, but no institution is too small to permit the development of a plasma supply suitable to its needs.

Too much emphasis has been placed on the various kinds of plasma, e.g., liquid, dried concentrated etc., and too little on the fact that there is fundamentally very little difference in them when therapeutic effectiveness is the prime consideration.

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ELECTROCARDIOGRAPHIC CHANGES AFTER ACUTE LOSS OF BLOOD *

By David Scherf, M.D., and S. D. Klotz, M.D., *New York, N. Y.*

Changes in the electrocardiogram following sudden blood loss have been observed with increasing frequency. The pioneer observations were casual and isolated, and the alterations were not distinguished from those noted in chronic anemias.[1, 3, 7, 11, 19] The abnormal electrocardiogram was usually ascribed to the anemia.

Recently Scherf, Reinstein and Klotz [17] reported abnormal electrocardiograms after profuse hemorrhage in gastric ulcer. The tracing was altered in 11 of 16 such cases, and the changes were pronounced in eight of them. The electrocardiogram became normal again within a few days. The hemoglobin level often had remained low or had fallen farther when the tracing reverted to normal. Moreover, blood transfusion did not influence the electrocardiogram. It was clear, therefore, that the changes were not due to the anemia. Reflex adjustment of the circulation following an acute loss of blood was considered responsible for the changes. The participation of the coronary arteries in the general vasoconstriction was presumed to create coronary insufficiency and a reduction of cardiac blood supply.

These studies have been continued, and the larger series now available permits some reference to the incidence of these changes as well as to the electrocardiographic pattern developing in acute blood loss from extragastric sources.

Results

Table 1 summarizes the observations in 26 cases of acute profuse hemorrhage. The first eight cases have been discussed elsewhere [17] and the last 18 are new. A determination of the hemoglobin seemed to provide more accurate clinical information concerning the amount of blood lost than measurement of the quantity of the vomited blood, for the melena frequently exceeded the hematemesis. The blood pressure and heart rate on admission or after the hemorrhage are indicated in the table and the presence or absence of shock is noted. Daily electrocardiograms were obtained. Reference is made to the type of alterations of the S–T segment and of the T-waves observed and to the time of the return of the normal electrocardiogram.

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TABLE I

No.	Name	Age	Estimated amount of blood loss	Hemoglobin		Blood pressure	Heart rate	Shock	Alterations of S-T segment in the four leads	Alterations of T-waves in the four leads	Duration of alteration in days	Clinical diagnosis; remarks
				On admission	On normalization of electrocardiogram							
1	R. P.	40	1000	25	—	80/45	144	+	− + − −	+ + − +	?	Peptic ulcer
2	T. K.	49	500+	20	32	100/68	110	+	− + + −	+ + + +	9	Peptic ulcer
3	B. A.	43	—	30	40	100/70	120	−	− − − −	+ + + +	7	Peptic ulcer
4	J. O.	48	500+	58	60	126/84	93	−	− − −	+ + +	—	Peptic ulcer
5	M. G.	29	—	76	—	110/70	100	−	− − − −	+ + + +	3	Peptic ulcer?
6	E. B.	61	1000	70	68	138/80	85	−	− − − −	+ + + +	7	Peptic ulcer?
7	C. A.	30	500+	72	62	138/36	65	+	− − −	+ + +	7	Peptic ulcer
8	J. W.	44	1500	75	78	150/80	96	−	− − − −	+ + + +	2	Peptic ulcer
9	D. H.	53	750	60	54	116/70	110	−	− − −	+ + +	2	Peptic ulcer
10	C. C.	58	—	23	—	80/50	106	−	+ + + +	+ + + +	—	Peptic ulcer, perforating with gaping blood vessel
11	G. I.	65	900	85	92	110/70	96	−	− − −	+ + +	9	Diverticulum of duodenum
12	J. W.	65	300+	60	56	126/80	130	−	+ + − −	+ + − −	2	Peptic ulcer
13	C. W.	75	650	34	40	40/?	92	+	+ + + +	+ + + +	3	Cirrhosis of liver
14	A. S.	49	850	60	—	90/64	130	+	− − − −	− − − −	—	Pneumoconiosis, tuberculosis; autopsy
15	H. O.	50	—	40	50	160/80	72	−	− − −	+ + −	3	Peptic ulcer?
16	O. F.	33	—	60	88	?	120	+	− − − −	+ + − −	5	Ectopic pregnancy, rupture
17	C. M.	49	1000+	55	—	190/70	136	−	− − − +	+ + + +	—	Peptic ulcer, autopsy
18	S. M.	33	450+	84	80	84/68	94	+	− − −	+ + +	2–3	Peptic ulcer
19	P. B.	70	300	50	64	170/80	82	−	− − − −	+ + + +	4	Peptic ulcer; malignancy?
20	M. L	44	800	64	60	128/98	132	−	− + + +	+ + + +	9	Peptic ulcer
21	G. J.	53	—	72	64	98/72	120	−	− − − −	+ + + +	3	Peptic ulcer
22	G. K.	53	1150	35	34	104/60	104	−	− ± −	+ + +	7	Peptic ulcer; autopsy
23	W. W.	54	350+	65	62	85/40	85	+	− + −	+ + +	2	Carcinoma of stomach
24	C. B.	58	300	70	65	86/60	92	+	+ + −	+ + +	7	Peptic ulcer
25	H. E.	60	400	58	33	135/85	100	−	− − −	− − −	—	Carcinoma of stomach
26	O. H.	65	—	37	33	102/42	80	−	− − −	+ + +	9	Carcinoma of stomach

Electrocardiogram. Usually a sinus tachycardia occurred after a hemorrhage. In the main when changes appeared, they involved the S–T segment and T-waves. Sometimes the QRS-complexes became lower (lower voltage). The S–T segment was depressed below the baseline and twice this depression was found in all limb leads and in a chest lead (CR_2); in 16 cases there was no S–T depression. More frequently the T-waves became lower, invisible, or even inverted. Although these changes disappeared completely within two days in six cases, a few days more were required in the remaining. In every instance the electrocardiogram became normal within nine days after the hemorrhage provided the patient survived and no second hemorrhage occurred. In one patient (case 8) who experienced a profuse hemorrhage exceeding 1500 c.c., an electrocardiogram taken seven hours after the episode revealed only slight changes, whereas the alterations were very pronounced in the tracing taken 18 hours after the hemorrhage. Accordingly the electrocardiographic alterations appear to develop slowly over a period of several hours.

Figure 1 depicts a typical series of electrocardiograms. This patient (case 20, table 1) suffered from upper abdominal post-prandial distress for many months. Two days before admission he vomited approximately 500 c.c. of bright red blood; another 300 c.c. were brought up shortly after admission. The hemoglobin on admission was 64 per cent, and the blood pressure was 128 mm. Hg systolic and 98 mm. diastolic. The next day these values were 62 per cent and 130 mm. Hg systolic and 86 mm. diastolic respectively; two days later they were 60 per cent and 120 mm. Hg systolic and 76 mm. diastolic.

The first electrocardiogram (figure 1*a*) was obtained on admission. There is a sinus tachycardia (rate 124), and abnormally low T-waves are visible in Lead I. On the following day (figure 1*b*) the rate was slower, the S–T segments in Leads II and III were markedly depressed, and the T-waves have disappeared in all limb leads. The T-wave has become inverted in the chest lead (CR_2). Two days later (figure 1*c*) the S–T segments were less depressed, and in four days the T-wave had become positive (figure 1*d*). On the ninth day after the hemorrhage the electrocardiogram was normal although the hemoglobin level was unchanged.

Since more pronounced changes disappeared more slowly than slight ones, the severity of the alteration is a factor in their duration. However, continuation of bleeding seems responsible for retarded recovery of the electrocardiogram in some cases. Twice a recurrence of hemorrhage coincided with the reappearance of abnormalities in the electrocardiogram.

A 53 year old man (case 21, table 1) was admitted because of hematemesis and tarry stools. He had suffered from upper abdominal pain after eating but obtained prompt relief with alkalies. The quantity of blood vomited could not be accurately determined. Physical examination of the heart was negative. The blood pressure was 98 mm. Hg systolic and 72

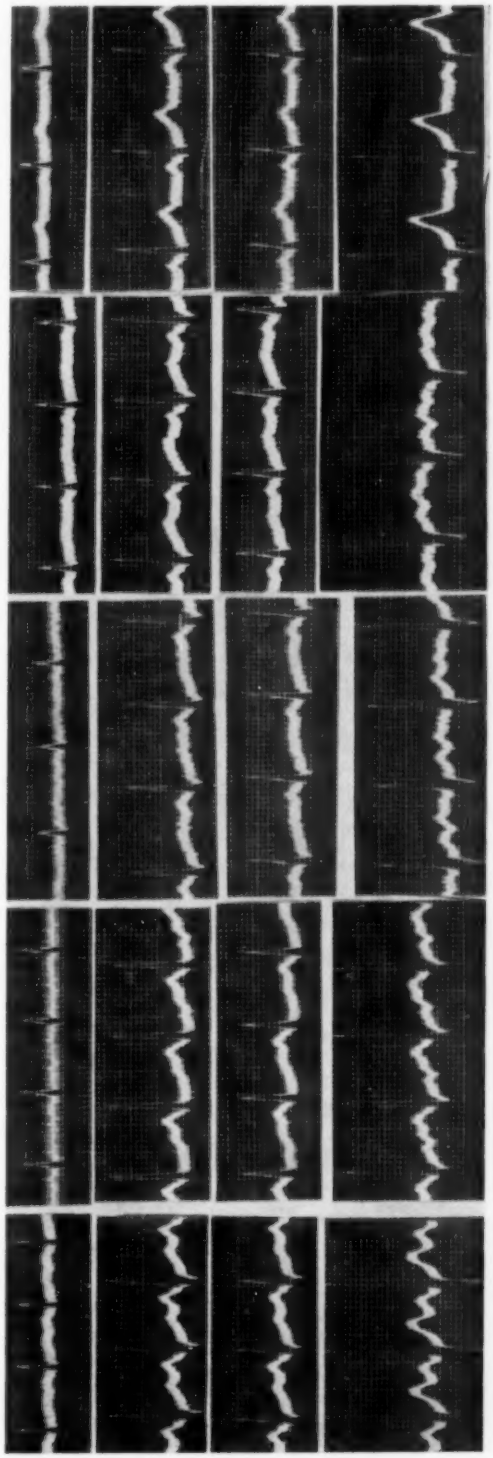


FIG. 1. Series of electrocardiograms obtained from a patient with gastric hemorrhage.

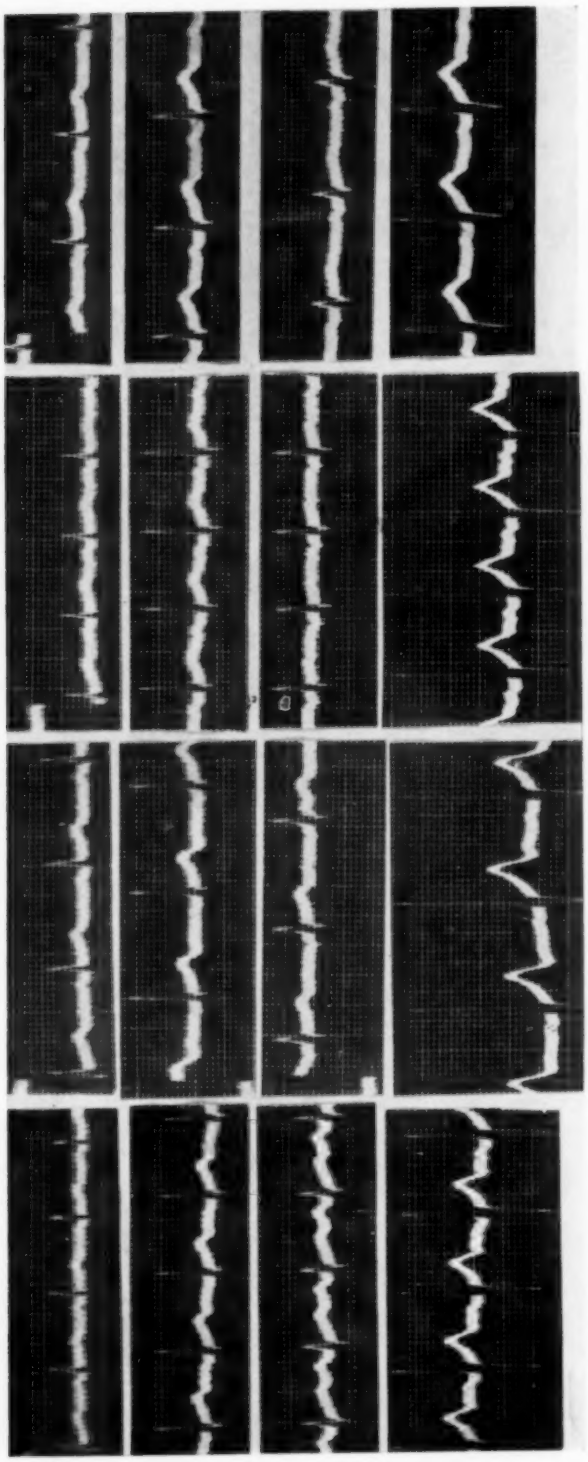
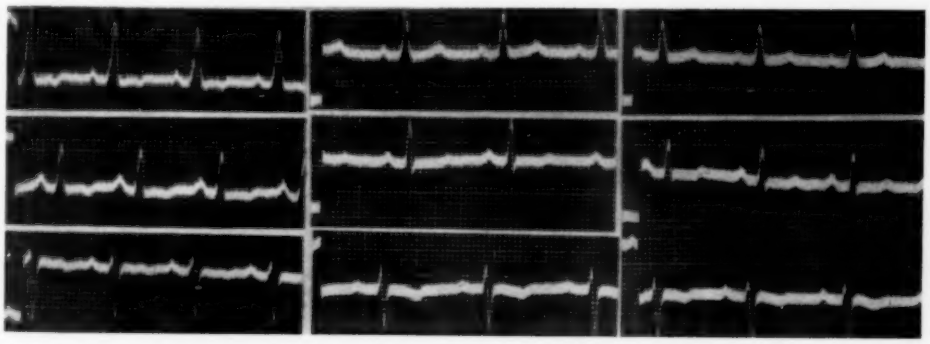


FIG. 2. (*a*) and (*b*) show the alterations in the electrocardiogram after the first, (*c*) and (*d*) after the second hemorrhage.

mm. diastolic, and the hemoglobin was 72 per cent. No shock was evident. The electrocardiogram (figure 2*a*) showed a sinus tachycardia (rate 115) with low T-waves in Lead I. The next day the rate was 83 and the T-waves in Lead I were normal (figure 2*b*). Shortly after this tracing was obtained, another hematemesis of 250 c.c. occurred, and a transfusion of 400 c.c. of blood was given. Twenty-four hours later the rate was 115 and low T-waves were noted in all limb leads (figure 2*c*). The tracing became normal within 48 hours (figure 2*d*). A similar return of pathological electrocardiographic findings after a second hemorrhage was seen in case 22.

In two cases the initial complex became wide, slurred and notched after a hemorrhage and reverted to normal as the T-waves regained their former appearance.

A 33 year old man was admitted for hematemesis and tarry stools. He had vomited about 400 c.c. of blood and was in mild shock with a blood



a *b* *c*

FIG. 3. Widening of the QRS-complex and abnormal T-waves following gastric hemorrhage.

pressure of 84 mm. Hg systolic and 68 mm. diastolic. The initial hemoglobin was 84 per cent, and it fell only two points in two days. His first electrocardiogram (figure 3*a*) was obtained 24 hours after the hematemesis. The heart rate was 94, the conduction time normal, and a left axis deviation was present. The QRS complexes measured 0.10 second and were split and slurred. The T-waves of Leads I and II were inverted. Four days later the initial complexes were less plump and T_1 and T_2 were positive (figure 3*b*). By the eleventh day after the hemorrhage the T-wave had undergone further improvement, and the width of the QRS complexes had diminished to 0.08 second (figure 3*c*). In another patient, who was 65 years old, the recovery required nine days.

Incidence of electrocardiographic changes. Originally 11 of 16 patients with gastric hemorrhage had electrocardiographic changes.[17] In the additional 18 consecutive cases definite alterations were noted in 16, but no changes were observed in a patient with pneumoconiosis and pulmonary

tuberculosis with fatal hemoptysis and in a patient with gastric hemorrhage due to carcinoma. The discrepancy in the two series and the higher incidence in the second are explained by the recording of daily electrocardiograms in the last series, the first being taken as soon as possible after the hemorrhage. When the first series was studied, four or five days often elapsed before the first electrocardiogram was secured so that alterations could have vanished. The high incidence of positive findings is remarkable and entitles them to be considered as one of the rather constant signs of profuse acute hemorrhage.

The relation between shock and the electrocardiographic changes. Table 1 indicates that shock is not necessary for the appearance of the electrocardiographic changes. No alterations or only slight ones occurred in the presence of shock (cases 14 and 16), whereas marked abnormalities were observed in its absence (cases 10 and 20). Naturally the electrocardiographic changes were decided in the presence of shock, but there is no proof for causal interrelation; both are consequences of the hemorrhage. The fact that shock per se may alter the electrocardiogram requires no discussion.

The relation between the amount of hemorrhage and the electrocardiographic changes. A final answer to this problem must await the application of exact methods of determining the blood loss. The results in table 1 suggest that in general the larger the acute loss of blood as indicated by the post-hemorrhagic hemoglobin level, the more marked are the electrocardiographic alterations. The opposite situation does not hold true, for pronounced changes are encountered when the hemoglobin remains above 80 per cent. In the two cases (table 1) without electrocardiographic changes the blood loss approximated 850 c.c. (case 14) and 400 c.c. (case 25).

In a ruptured ectopic pregnancy (case 16) only slight electrocardiographic changes appeared although blood loss was great and the hemoglobin fell to 40 per cent. Furthermore the electrocardiogram returned to normal within a few days in most of the cases although the hemoglobin underwent additional reduction or remained low. It is the acuity of blood loss rather than the absolute amount lost which is decisive.

Many observations emphasize that a marked but slowly progressive chronic anemia frequently does not alter the electrocardiogram despite remarkably low hemoglobin values.[14, 15]

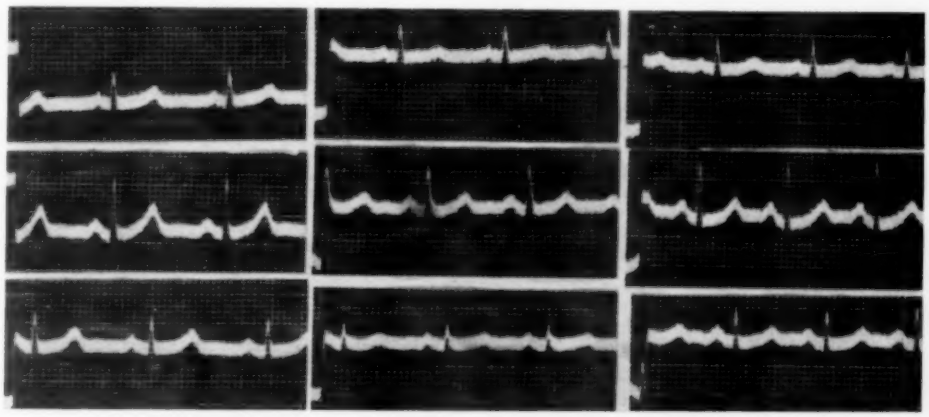
The rôle of age. The age of the patients varied between 29 and 70 years. Although age did not seem to have any important influence on the incidence of electrocardiographic changes, the series is too small to permit any sweeping conclusions.

The influence of phlebotomy on the electrocardiogram. The etiology of the hemorrhage ought not to have great importance in accounting for the high incidence of changes found in the electrocardiogram, although most of our cases suffered from bleeding peptic ulcers. In hemoptysis resulting from pulmonary tuberculosis (case 14) no changes were observed, but they were

noted in conjunction with a hemorrhage from an esophageal varix (case 13) and in a ruptured ectopic pregnancy (case 16). In order to study the effect of acute blood loss evoked by other mechanisms than hematemesis and to observe the results of minor bleeding, the influence of phlebotomy on the electrocardiogram was studied in a series of cases.

It has been previously reported that electrocardiographic alterations do appear in dogs [10] and rabbits [16] following large phlebotomies. The changes consist of lowering or inversion of the T-waves and low voltage.

Phlebotomy was performed in 33 patients whose ages varied between 32 and 83 years. Most of them were hypertensives. The data obtained from this study are summarized in table 2, and it will be noted that changes in the



a *b* *c*

FIG. 4. Lowering of the T-waves following phlebotomy in a patient with a normal electrocardiogram.

electrocardiogram were observed in only 8 of 33 cases. In this series as well the effect was manifested mostly on the T-waves which became lower or inverted. Only those patients whose electrocardiograms were already abnormal (evidence of left ventricular strain resulting from hypertension) presented increased depression of the S–T segment in Leads I and II after phlebotomy.

The changes which appeared after phlebotomy in a 63 year old patient (case 29, table 2) are reproduced in figure 4. Arteriosclerotic peripheral vascular disease without evidence of coronary involvement was responsible for his admission. Before phlebotomy the electrocardiogram was normal (figure 4*a*). Twenty-four hours after a phlebotomy of 450 c.c. the T-waves were definitely altered in each lead, whereas the S–T segments remained unchanged (figure 4*b*). The electrocardiogram was practically normal in 48 hours after the venesection. Whenever bleeding lowered the height of the T-waves in this series, the changes disappeared within two or three days.

TABLE II

No.	Name	Age	Diagnosis	Amount of phlebotomy in c.c.	Electrocardiogram before phlebotomy	After 1 hour	After 24 hours
1	A. T.	42	Essential hypertension	750	Normal	No change	No change
2	S. M.	65	Atheromatosis, hypertension	500	Low T_1 Deep Q_3	No change	No change
3	L. T.	73	Atheromatosis, hypertension	500	Normal	No change	No change
4	J. O.	64	Osteo-arthritis	800	Normal	No change	No change
5	V. D.	58	Polycythemia vera	1000	Normal	No change	No change
6	S. B.	76	Arteriosclerosis	500	Low T-waves	No change	No change
7	D. M.	68	Atheromatosis, hypertension	500	Complete heart block	No change	No change
8	S. H.	68	Hypertension	500	Normal	No change	No change
9	A. S.	48	Fibrotic tuberculosis	700	Right ventricular strain	No change	No change
10	C. B.	67	Hypertension	500	Low T-waves	No change	No change
11	V. M.	55	Essential hypertension	400	Normal	No change	No change
12	V. F.	83	Atheromatosis	500	Left ventricular strain	No change	No change
13	G. D.	57	Hypertension	600	Left ventricular strain	No change	No change
14	J. T.	48	Hypertension	500	Deep Q_3	No change	No change
15	L. L.	65	Atheromatosis, hypertension	500	Low T-waves, left axis deviation	No change	No change
16	S. D.	60	Mild hypertension	500	Left axis deviation	No change	No change
17	T. S.	53	Essential hypertension	500	Left axis deviation	No change	No change
18	M. R.	80	Atheromatosis, hypertension	500	Left axis deviation	No change	No change
19	J. R.	65	Hypertension	500	Left axis deviation. Low T_1	No change	No change

TABLE II—*Continued*

No.	Name	Age	Diagnosis	Amount of phlebotomy in c.c.	Electrocardiogram before phlebotomy	After 1 hour	After 24 hours
20	M. P.	52	Arteriosclerosis	500	Left ventricular strain	No change	No change
21	S. G.	68	Atheromatosis, hypertension	500	Deep Q_3	No change	No change
22	A. K.	82	Atheromatosis, hypertension	500	No T-waves	No change	No change
23	G. O'S	57	Mild hypertension	750	Low T_1; deep Q_3	No change	No change
24	H. M.	62	Hypertension	500	Left axis deviation. No T_1	No change	No change
25	C. V.	32	Psychoneurosis	650	Normal	No change	No change
26	N. C.	68	Arteriosclerosis, hypertension	500	Left axis deviation	T_1 inverted	T_1 inverted
27	M. C.	54	Cerebral hemorrhage, hypertension	800	Normal	T_1 definitely lower	Same
28	C. F.	64	Atheromatosis	500	Low T-waves, S-T segment depressed	T_2 and T_3 lower, S-T more depressed	
29	A. F.	63	General arteriosclerosis	450	Normal	No change	T_1 and T_3 lower
30	L. B.	61	Mild hypertension	500	S-T in Lead I slightly depressed	S-T more depressed	T_1 inverted T_2 lower
31	H. J.	46	Hypertension, coronary sclerosis	1000	Left axis deviation, low T-waves, depressed S-T	T_1 lower, S-T much more depressed	T-waves inverted
32	J. R.	35	Gastritis	750	Normal	T_1 and T_2 lower	Same
33	M. T.	38	Malignant nephrosclerosis	800	Left ventricular strain	Same	T_1T_2 more inverted — Less inversion of T-wave 5 hours after phlebotomy

The alterations after phlebotomy were more marked in cases with an abnormal electrocardiogram. This is exemplified by the tracings of a 38 year old patient (case 33, table 2) who suffered from a compensated "malignant" hypertension. His electrocardiogram showed the pattern of a left ventricular strain with inversion of T-waves in Leads I and II (figure 5*a*). A tracing obtained one hour after the removal of 800 c.c. of blood failed to disclose any changes. In five hours the T-waves were less inverted in Leads I and II (figure 5*b*) but the inversion increased 24 hours later (figure

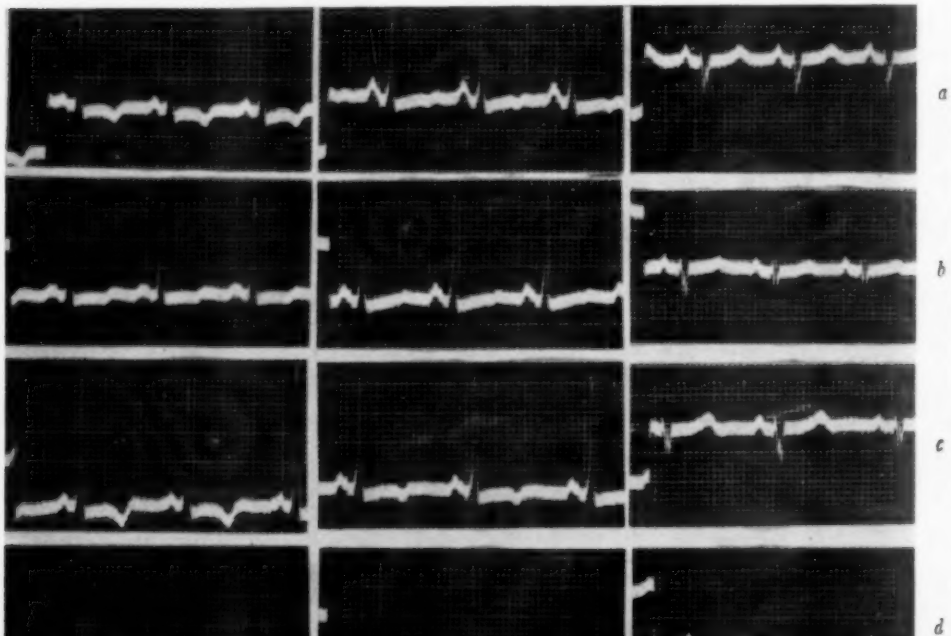


FIG. 5. Changes of the T-waves after phlebotomy in a patient with an abnormal electrocardiogram.

5*c*). Within another 48 hours the electrocardiogram reverted to the pre-phlebotomy status (figure 5*d*).

The tendency of the T-waves to become higher when formerly positive or less inverted if negative prior to phlebotomy was observed in two other cases in the five-hour tracings. An increased output of epinephrine may be responsible.[12]

Initial electrocardiographic changes were found as early as one hour after phlebotomy. Three out of the eight patients who showed alterations in the electrocardiogram after phlebotomy had a normal electrocardiogram previously (table 2); 10 of the 25 cases who did not show changes after the

phlebotomy had a normal electrocardiogram. In four of the eight positive cases the amount of blood removed did not exceed 500 c.c. In seven of 25 cases in which phlebotomy failed to induce changes in the electrocardiogram, more than 500 c.c. of blood had been taken in each instance. One patient who suffered from polycythemia vera failed to exhibit changes, although the phlebotomy amounted to 1000 c.c. The change in blood pressure provoked by the phlebotomy never exceeded 15 mm. Hg.

Accordingly one may conclude that after a large phlebotomy and especially when the patient had an abnormal electrocardiogram prior to the venesection, alterations of the final deflection appeared occasionally; altogether they were found in eight of 33 cases. Electrocardiographic changes appeared after the removal of 450 c.c. of blood yet failed to occur after the loss of 1000 c.c. Such individualization of response must be expected in a biological experiment. The changes in the electrocardiogram usually vanished in 24 to 48 hours.

Discussion

Fourteen patients in a consecutive series of 15 developed definite transitory changes in the electrocardiogram after a profuse gastric hemorrhage. Similar changes were encountered in two out of three cases of acute blood loss of other than gastric origin. An investigation of the electrocardiographic alterations after phlebotomy revealed that changes may appear after the loss of relatively small amounts of blood. These alterations, within certain limits, are independent of shock or marked anemia.

The incidence of electrocardiographic alterations indicates that after blood loss the coronary arteries participate in the general vascular spasm which involves the arterioles to a greater extent than previously conceived.[2] Owing to the increased outpouring of adrenalin [20] the heart requires a larger amount of oxygen, whereas the supply is actually diminished. A necrosis of myocardial fibers, histologically demonstrable,[5] or a local change of electrolytes consisting of hyperpotassiumemia [6] and not susceptible to visualization in microscopic sections may be produced. Either would induce electrocardiographic changes. Perhaps the mechanism of the development of myocardial necroses is akin to the well known necroses of the liver or duodenum after an acute severe hemorrhage.[13]

Apart from the rapidity and quantity of blood loss, other factors such as the activity and responsiveness of vascular reflexes play an important rôle and influence the occurrence and severity of the electrocardiographic alterations.

In discussions of the vascular changes following an acute hemorrhage the conception is frequently offered that narrowing of the arterioles in the systemic circulation is protective and is designed to ensure an adequate blood supply to vital organs such as the heart, central nervous system and kidneys. The facts presented in this paper indicate that the protection is incomplete

since the coronary vessels participate in the general constriction of the arteries and perhaps to a greater degree than some others.

Cardiac symptoms are not an uncommon consequence of an acute hemorrhage. A sensation of oppression, palpitation, anginal pain, sweating may be prominent at this time. In such patients the internal hemorrhage may not be discovered by the examining physician if hematemesis or melena is not observed. If an electrocardiogram is taken and the alterations suggest "myocardial damage," an erroneous diagnosis of coronary sclerosis is occasionally made. The co-existence of an anginal syndrome and electrocardiographic changes makes the mistake understandable.

Internal postoperative hemorrhages may be difficult to distinguish from pulmonary embolism. In the former anginal pain is not rare and the blood loss need not provoke decided anemia yet electrocardiographic changes may appear. In pulmonary embolism as well as in internal hemorrhage, hypotension, anginal pain, tachycardia, perspiration, the shock syndrome and electrocardiographic changes are found. Although the alterations of the electrocardiogram tend to follow a definite pattern in pulmonary embolism,[9] the changes frequently mimic those encountered after hemorrhage.[18]

It should be stressed that the electrocardiographic changes after an acute hemorrhage ordinarily are limited to the T-waves; only in severe cases does depression of the S–T segment also appear. The latter phenomenon is found regularly when anoxia of the myocardium is widespread. Since this sign is frequently absent after an acute hemorrhage, one may presume that only small zones of heart muscle are affected in the majority of cases, possibly the subendocardial layers in the vicinity of the papillary muscles, for they are known to be the most sensitive to diminution of cardiac blood supply.

The typical electrocardiographic changes may recur after a second hemorrhage even when the tracing has just become normal after the first hemorrhage.

The rapidity with which the electrocardiographic abnormalities disappear, often within two to three days, does not militate against the existence of small necrotic areas. If subendocardial tissue is damaged mechanically in experiments on the exposed dog heart,[4] the alterations which appear simulate those described in this paper and resemble those appearing in coronary insufficiency of other origin. These changes may disappear within a few minutes.

Summary

Fifteen cases of profuse gastric hemorrhage are reported. All but one showed alterations of the T-wave, and some of the S–T segment as well, if electrocardiograms were taken soon after the hemorrhage and daily thereafter. Of three cases of hemorrhage from other sources, two presented similar electrocardiographic alterations.

The first changes to appear were lowering of the T-waves. More advanced alterations consisted of disappearance or inversion of these waves and depression of the S–T segment. Slightly lowered voltage of the QRS complex was occasionally observed.

The changes in the electrocardiogram vanished in two to nine days.

They developed in the absence of shock and without severe anemia and were independent of the hemoglobin level.

The effect of phlebotomy on the electrocardiogram was studied in 33 cases. Alterations were observed eight times. Although they may develop after the removal of 450 c.c. of blood, they may not appear with a venesection of 1000 c.c.

The appearance of electrocardiographic changes after an acute blood loss has particular importance in the differential diagnosis between internal hemorrhage with cardiac symptoms and the cardiac manifestations associated with coronary thrombosis and pulmonary embolism.

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PRIMARY CARCINOMA OF THE LIVER*

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Primary carcinoma of the liver is alleged to be a rare disease in North America and Europe. In other parts of the world and especially in the Orient and South Africa it is said to occur much more commonly. Our interest in the disease has been stimulated by this apparent curious variation in geographical distribution, and because we recently have had under our observation several cases of the disease presenting unusual clinical and pathological manifestations. Although there are in the literature many excellent papers dealing with reports of single cases and of numerous series of cases, as well as of reviews of the literature on primary carcinoma of the liver, we feel that a number of our cases present features of such unusual interest as to warrant publication of them, along with a brief survey of all of the cases in the records of the Department of Pathology of the Stanford University School of Medicine.

The difficulty of establishing reliable diagnostic criteria for the disease and consequently of arriving at a correct clinical diagnosis has prompted us to review the subject in general and to scrutinize the various cases we have had the opportunity of studying. Among these cases are those of a neonatal hepatic carcinoma associated with metastasis to the humerus, primary carcinoma occurring coincidentally in the livers of two non-related negroes who were the same age and who had lived together in the same boarding house for a number of years, and an instance in which the disease was accompanied by periods of prolonged hypothermia. In three cases of hemochromatosis in which there was associated primary carcinoma of the liver it was observed that although the tumor cells were demonstrated to store fat and to produce bile, in no instance was there storage of iron containing pigment. Other points of particular interest include the frequency with which the disease occurred among Chinese, the frequent association of it with cirrhosis of the liver, and the increasing incidence of cirrhosis since repeal of prohibition.

Review of the cases in our series indicates that the most important coexisting or perhaps contributing factor in the development of primary carcinoma of the liver is antecedent damage to the liver. In most instances this change is characterized by the presence of cirrhosis in all degrees from mild, so-called limited cirrhosis, to far advanced atrophic cirrhosis of Laen-

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nec. In some instances damage to the liver was on the basis of toxic necrosis with subsequent healing and nodular hyperplasia.

Literature

The literature on primary carcinoma of the liver is fairly extensive and may profitably be divided into (1) the older literature dealing principally with individual and collected case reports and studies of the incidence and types of pathologic lesions observed in these cases, and (2) the more recent literature dealing with experimental phases of the disease and the possible relation of it to preëxisting damage to the liver induced by hepatotoxic substances and dietary deficiencies.

An excellent summary of literature on the clinical and pathologic phases of the disease was presented in a 10 year collective review published by Greene [1] in 1939. In summary Greene reports that (1) primary carcinoma of the liver may be found at any age, but most often between 50 and 60; (2) it is found most often in males; (3) it is not so infrequent as formerly believed; (4) it occurs more often among Asiatic peoples; (5) the cause of it is unknown but irritation of the liver seems to play an important rôle; (6) hepatomata far outnumber cholangiomata; (7) regional and intrahepatic metastases are common, but distant metastases fairly uncommon; (8) preoperative diagnosis seldom is made because of multiple and unrelated symptoms; (9) the duration of disease is short; (10) lobectomy is of doubtful therapeutic value.

The variation in geographical distribution of primary carcinoma of the liver is quite well recognized at present. Among some races (Chinese and Bantu) and in certain localities (Japan and South Africa) cancer of the liver is much more prevalent than elsewhere. According to Nagayo,[2] in Japan primary carcinoma of the liver ranks third in frequency of occurrence in males (6.7 per cent) and sixth in females (4.6 per cent). In China hepatic cancer ranks fifth in males (8.1 per cent) and eighth in females (5.6 per cent) and in Korea it ranks third in males (9.8 per cent) and fourth in females (6.6 per cent). The prevalence of the disease among Filipinos is demonstrated by the incidence of the disease at the Manila General Hospital as cited by Reed [3] and De Leon.[4] Of 1,502 cases of malignant tumors admitted to the Philippine General Hospital in 1910–1914 and 1922–1926, 95 or 6.32 per cent were primary carcinoma of the liver. It is alleged that primary carcinoma of the liver is especially common among hybrid Chinese and Filipinos.[3] In the Memorial Hospital of New York City during 1917–1929 the incidence of such tumors was 0.17 per cent in a series of 19,129 patients with neoplastic diseases (Pack and LeFevre [5]).

Japanese investigators have been prompted to institute a survey for an explanation of the fact that, in contrast to experience in other countries, primary carcinoma of the liver ranks as one of the leading factors contributing to mortality from cancer in Japan. Recognition of the cancero-

genic properties of the azo-dyes has caused especial scrutiny of p-dimethyl-amino-azobenzene, better known as "butter-yellow." Experimentally in laboratory animals "butter-yellow" is an especially potent chemical in the production of liver tumors. Oral administration of "butter-yellow" to rats in concentration of 2 to 3 per cent in olive oil causes carcinoma of the liver, and occasionally of the stomach. Two other closely related azo-compounds, o-amino-azotoluene, and 4'hydroxy, 2:3 azotoluene injected into pure strain mice give rise in a large percentage of cases to transplantable liver cell carcinoma, but no tumor at the site of injection. The oral administration of 4'hydroxy, 2:3 azotoluene into rats causes tumor of the bladder, but none in the liver. The use of "butter-yellow" as a coloring agent in the Japanese diet may possibly be a factor which has contributed to the high incidence of primary cancer of the liver in Japan. The results of Japanese workers have been confirmed by Orr [6] who has studied the histology of the liver of the rat during the course of carcinogenesis induced by "butter-yellow." Orr expressed the opinion that the primary effect of "butter-yellow" on the liver parenchyma is destructive and that proliferative changes are in the nature of regeneration.

Among the Chinese and other Oriental races the prevalence of parasitic infection (especially liver flukes, *Taenia crassicollis* in rats, schistosomiasis) is loosely cited as another possible factor contributing to the higher incidence of primary carcinoma of the liver among these races.

The incidence of carcinoma of the liver among certain tribes in South Africa has been reported by Prates [7] in a series of 85 cases among members of the Bantu race. The clinical picture presented is similar to that observed in the United States, but interestingly enough the diagnosis commonly was made clinically. Prates [7] reports that primary carcinoma of the liver occupies first place in the list of neoplasms, and that it affects especially young and healthy individuals. Although the incidence of parasites in the cases reported by Prates [7] was extremely high, it was believed that parasitism was not a significant etiologic factor since parasitism exists throughout the tropics in such a high incidence in other tribes without being associated with primary carcinoma of the liver. The possibility of a dietary factor as an important etiologic agent is considered in this group of Bantus.

Further evidence of the importance of the dietary factor in the possible development of primary cancer of the liver is offered by the experimental studies of Kinosita,[8] who in 1940 reported that rice-bran oil could definitely hinder the production (by injections of "butter-yellow") of cancer of the liver. Kensler and his co-workers,[9] in further studying this problem, found evidence to suggest that riboflavin deficiency coincided with susceptibility to the carcinogenic effect of "butter-yellow" although oral administration of 5 milligrams of the vitamin daily was almost without protective effect. Casein administered along with riboflavin gave rather striking protection against cancer of the liver produced by "butter-yellow." More recent studies

of Sugiura and Rhoads [10] on this problem indicated that rice-bran extract and small amounts of ether extract of yeast possessed a transient inhibiting effect on cancer of the liver induced in rats by "butter-yellow." A diet of unpolished rice containing 15 per cent of brewers yeast apparently completely inhibited the development of this type of cancer, an effect which diminished when the basal diet of "butter-yellow" rice contained less than 15 per cent yeast. The addition of purified casein to the "butter-yellow" rice diet had no inhibiting effect.

Material Studied

The study we have made is based on a total experience of 49 cases of primary cancer of the liver. All of these cases are in the records of the Department of Pathology of the Stanford University School of Medicine. During the interval between 1898 and May 30, 1942 * there have been 11,045 autopsies recorded in the department which makes an incidence 0.444 per cent for primary carcinoma of the liver. This compares with the reports of Rowen and Mallory [11] of an incidence of 0.138 per cent or nine cases out of 6,500 autopsies, of Loesch [12] of 0.467 per cent or 14 cases out of 3,000 autopsies, of Charache [13] who in a series of collected cases reported an incidence of 0.56 per cent or 808 primary carcinomata of the liver in 159,762 autopsies, and of 0.17 per cent in 19,129 patients with neoplastic diseases in the Memorial Hospital in New York City (Pack and LeFevre [5]).

Complete reports are available on the gross and microscopic studies of the tissues in all of the 49 cases and in 40 of them clinical data are available also and serve as the bases for the clinical data reported in this study.†

Clinical Data

The essential clinical data for the 40 cases are summarized in table 1.

From the clinical standpoint the most commonly observed symptoms and striking findings in this disease are abdominal pain, jaundice, ascites, weight loss, and a palpable abdominal mass. It is interesting that among the most common clinical features of carcinoma of the pancreas are abdominal pain, an abdominal mass, and nondescript digestive symptoms (Eusterman and Wilbur [14]). Unlike carcinoma involving the muscular tube of the digestive tract, primary neoplasms in the liver and pancreas do not often produce anemia until late in the course of the disease.

* In this interval the total number of autopsies was 11,469. This total has been corrected by 424 cases, originally deleted from the first part of the series by Dr. William Ophuls in "A Statistical Survey of Three Thousand Autopsies," Stanford University Press, 1926. These cases were omitted because of the absence of microscopic examination of tissues (in the early years). All cases in our series are ones with both gross and histologic studies. Not included in our series are two classical descriptions of gross material of cases of carcinoma of the liver antedating our present statistical records.

† We are obliged to Dr. A. C. Reed of San Francisco for the clinical data in one of the cases.

Abdominal Mass. An abdominal mass was palpated in 31 or 77.5 per cent of the cases. In almost all instances the mass was in the right upper quadrant of the abdomen and easily recognized as an enlarged liver. It was usually firm, often irregular and nodular, and generally only slightly if at all tender.

TABLE I

Primary Carcinoma of the Liver

Analysis of Clinical Data in 40 Cases

Symptoms	Number of Cases	Per Cent of Cases
Abdominal mass	31	77.5
Abdominal pain*	29	72.5
Jaundice	24	60.0
Ascites	24	60.0
Weight loss	21	52.5
Peripheral edema (legs)	17	42.5
Alcoholism	9	22.5
Gross bleeding		
(*a*) Recurring epistaxis	4	
(*b*) Hematemesis	2	
(*c*) Melena	1	
Parasites in intestine	0	
Clinical diagnosis**	12	30.0

* In only three cases was it definitely stated that pain did not exist.
** Diagnoses made or strongly suspected clinically or at operation.

Abdominal Pain. Pain in primary carcinoma of the liver rarely is severe, but it is the most common symptom in our experience. In fact, in only three of our cases was it definitely stated that pain did not exist. The pain generally was located in the epigastrium or beneath the right costal margin. It not infrequently was present in or referred to the back, and it generally was described as a dull heavy ache, fairly constant in occurrence and rarely of severe degree until late in the disease. The cause of the pain in carcinoma of the liver is not clear, but one would suspect that it most likely has to do with enlargement of the organ and distention of its capsule. Certainly from the diagnostic standpoint the pain of this disease is not characteristic or diagnostic.

Symptoms of Indigestion. Symptoms of indigestion were not common in these patients provided abdominal pain is not included. In those cases in which it was present it was nondescript in character and no definite symptom complex could be determined to be characteristic of the disease.

Jaundice. In 24 cases or 60 per cent jaundice was present at the time the patient first was examined or it developed subsequently in the course of the disease. It is rather striking that in almost half of the cases jaundice was absent during the entire clinical course of the disease. The degree of jaundice present was variable with icterus index values of 10 to 176 units. In all except three instances the icterus index was less than 100 units suggesting that the jaundice in this disease generally is not intense but, in fact, mild.

Ascites. Ascites was present or developed in 24 or just over one-half of the cases (60 per cent). In quite a few cases it was necessary to tap the abdomen once or more often and in several cases the fluid was bloody in appearance. In no instance in which it was studied were malignant cells found in the ascitic fluid. Ascites generally was associated with diffuse hepatic damage (cirrhosis), with thrombosis of the portal vein or with a combination of the two.

Loss of Weight. In approximately half the patients loss of weight was a prominent feature (21 cases—52.5 per cent). In only two cases was this the presenting complaint.

Peripheral Edema. In 17 cases (42.5 per cent) there was associated edema of the legs. Unfortunately studies of the plasma protein values were not made in most of these cases and the importance of a low value for plasma protein as a causative factor of the edema cannot be estimated. Undoubtedly pressure of an enlarged liver on the inferior vena cava or involvement of the vena cava by tumor or thrombus formation were important factors in producing edema which almost always involved the lower extremities only.

Bleeding. In a few instances only was bleeding a prominent symptom until the time of death. There was recurring epistaxis in four cases, and hematemesis and melena in three cases only. Fatal bleeding from esophageal varices occurred only twice and fatal epistaxis only once. However, bleeding into the peritoneum was common and manifested clinically by a finding of grossly bloody ascitic fluid and pathologically by actual gross blood in the peritoneal cavity of 12 of the total series of 49 cases (24 per cent) in an amount sufficient to lead the pathologist to consider bleeding as a factor of importance in contributing to the death of the patient. This bleeding generally occurred from the surface of the liver as a result of involvement of it by the neoplastic process. This finding is in keeping with the observations of Mathews [15] who reports that fatal bleeding from varices and from tumors perforating the capsule of the liver is common. Unfortunately studies of the prothrombin content of the plasma were made in a few of the recent cases only and a statement cannot be made of the possible relationship of deficiency of vitamin K to bleeding in this series of cases.

Alcoholism. In only nine or 22.5 per cent of the cases is it definitely known that alcohol was used in considerable quantities over a period of time. The importance of this factor cannot be evaluated but the increase in cirrhosis of the liver since the repeal of prohibition and the frequency of carcinoma of the liver in cirrhosis suggests that an increasing number of cases of primary carcinoma of the liver may be observed in the future. To date such a secondary rise has not been observed by us.

Blood. In 11 cases (27.5 per cent) the hemoglobin was less than 70 per cent (Sahli). In 19 instances the leukocyte count totaled 10,000 or more. The significance of this latter finding is not apparent unless it is a

manifestation of the malignant disease itself or of extensive disease of the liver or both. In seven cases the Wassermann reaction of the blood was positive.

Urine. In general urinalysis was essentially normal except for the presence of bile and of moderate amounts of albumin.

Roentgenologic Findings. Roentgenologic study of the patients in this series was rather disappointing as a diagnostic procedure. This is to be expected in view of the difficulty of visualizing changes other than those in the size of the liver. However, evidence of an enlarged liver was reported in six cases whereas in others the right dome of the diaphragm was found to be high. In most cases in which it was done, examination of the gastrointestinal tract did not reveal evidence of significant disease. Unfortunately cholecystograms were not done in a sufficient number of patients to permit any conclusion as to the value of this method of examination as a diagnostic procedure. The presence of jaundice in 60 per cent of the cases would tend to render this method of examination a useless one.

Incidence of Clinical Diagnosis. The antemortem diagnosis of primary carcinoma of the liver, or a very strong suspicion of it, was made in 12 of the cases (30 per cent). This figure is high because in three of the cases the diagnosis was made by biopsy at operation and in a fourth case by a biopsy taken during peritoneoscopy. In nine cases the clinical diagnosis was made of cirrhosis of the liver. Other diagnoses varied considerably.

Examination of the Stools. Examination of the stools for parasites failed to reveal evidence of parasitism in any instance. Occult blood was not uncommonly present in the stool but such a finding in the absence of careful observation and study while the patient partakes of a meat-free diet is of very questionable diagnostic value. In an occasional case excess amounts of fat were found in the stools but the significance of this could not be determined.

Tests of Liver Function. Tests of liver function were not performed in a sufficient number of cases to warrant any statistical treatment or conclusions.

Course of the Disease. It seems generally agreed that the clinical course of primary cancer of the liver is short. This has been our experience. Once the symptoms have developed to the point that an abdominal mass is palpable and there is jaundice and ascites the course generally is one of a few months only. In a few instances, such as that reported in case 1, the clinical course was considerably longer.

Well Differentiated Liver Cell Carcinoma in a Male Aged 19 Characterized Clinically by Hypothermia.

Case 1 (9C–46). The patient, a male 19 years of age, entered the hospital in October, 1938 because of emaciation, a protruding tumor mass in the right upper quadrant of the abdomen and periodic diarrhea. He had been in good health until June, 1937 at which time there developed fever, periodic diarrhea and pain in the

right flank. A moderate degree of anemia was present (hemoglobin 60 per cent). Because of failure of the gall-bladder to visualize on roentgenologic examination and subsequent enlargement of the liver surgical exploration of the abdomen was performed. It was reported to reveal necrotic lesions of unknown origin in the liver. Two months later after a stormy clinical course exploration again was carried out without any additional information being obtained. It was considered that an unusual infection of the liver was present. The course was gradually downward. In January, 1938 biopsy was made of a mass protruding as a tumor from the abdominal incision. It was reported to be a "hepatoma."

Ten months later when the patient came under our care the appearance of this mass was as noted (figure 1). Examination showed the patient to be weak, emaciated and pallid. There was marked dilatation of the superficial veins of the abdominal wall and an extremely large liver with a draining, fungating mass protruding from the scar of the abdominal incision. Ascites was absent, but slight edema of the feet was present.

Studies of the blood revealed the hemoglobin to be 54 per cent (Sahli), erythrocytes numbered 4,050,000 and leukocytes 12,500 per cubic millimeter of blood. Examination of the urine was negative. The Wassermann test of the blood was negative and the serum protein 4.7 gm. per cent. Roentgenologic studies of the chest revealed three small distinct nodules in the parenchyma of the lungs; those of the liver and spleen after intravenous injection of thorotrast showed an enlarged spleen; the liver failed to visualize. Biopsy of the fungating mass was reported as primary carcinoma of the liver.

There was gradual failure and death in January, 1939 following 12 hours of intermittent convulsive seizures.

The significant findings at postmortem examination were as follows: emaciation, dilated superficial abdominal veins, edema below the costal margins, and a protruding abdominal tumor mass. The peritoneum was smooth and glistening except for that covering the cul-de-sac and sigmoid which presented numerous flat pinkish-white tumor implants. There were three distinct tumor nodules (largest 1.0 cm. diameter) in the left lung. Varices were not present in the esophagus or stomach. The liver weighed 5000 grams, filled the entire upper abdomen, and the entire right lobe was replaced by tumor tissue. This tumor mass measuring 18 cm. in diameter was fairly discrete. There were other numerous satellite tumor masses in the liver, some of them compressed by the large growth (figure 2). The masses of tumor contained pink-gray, fairly firm tissue, areas of recent hemorrhage, and areas of golden-yellow necrosis. The large mass was directly connected with the mass of tumor protruding from the wound. The uninvolved liver tissue was dark purple in color and in one localized area only was evidence of jaundice present. The gall-bladder, bile ducts and portal vein appeared normal. The inferior vena cava and both renal veins were filled with thrombus.

Histologic study of the tumor showed liver-like cells forming cords and sheets of rather large polyhedral cells varying somewhat in size. There was no semblance of lobule formation, but capillaries ran between the cords (figure 3). Bile ducts were not seen. The cytoplasm was eosinophilic, and the nuclei large with exceedingly large nucleoli. Mitotic figures were rather infrequent. The cells were rich in glycogen.

FIG. 1. Photograph of fungating tumor protruding from abdominal wall at old operative site. Infra-red light accentuates venous markings showing marked dilatation of subcutaneous veins over chest wall and abdomen. Note widening of rib cage and emaciation. (Case 1)

FIG. 2. Transverse section of liver. Practically entire right lobe is occupied by huge tumor measuring 18 cm. in diameter. One dark lobule near upper inner portion is bile stained. (See figure 3.) Satellite tumors in right lobe as well as large 10.0 cm. tumor in left lobe. Intervening parenchyma shows no gross scarring or nodulation. (Case 1)

FIGS. 1–2.

Many of the cells presented various stages of necrosis, but in only a few of them were tiny fat droplets present. In some areas phagocytic cells resembling Kupffer cells contained granular thorotrast. The delicate fibrous tissue supporting stroma contained scattered hemosiderin-laden phagocytes. There was very little encapsulation of the tumor from the adjacent liver tissue. A section from the jaundiced spot showed the tumor cells rich in bile "sausages" (figure 3). In this area the supporting fibrous tissue stroma was more dense. The liver apart from the tumor showed moderate congestion of the central veins and sinusoids with many Kupffer cells

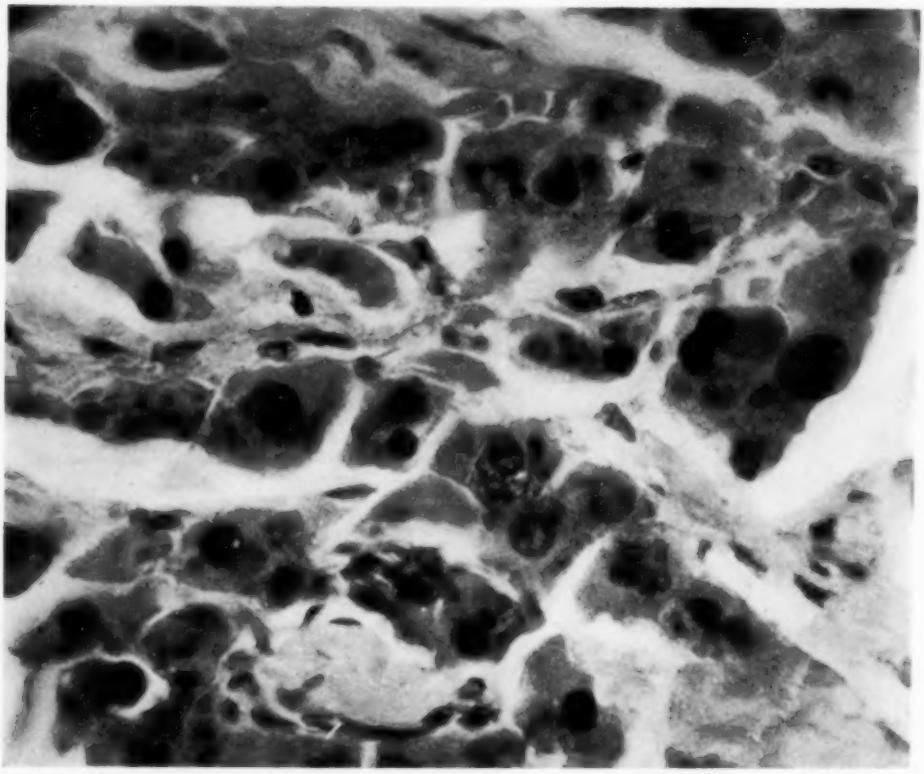


FIG. 3. Bile stained tumor nodule seen in figure 2. Note the cuboidal to polygonal shape of the tumor cells and the active production of bile in their cytoplasm. (Case 1.) (× 800)

filled with thorotrast. There was no bile in the cells or ducts. The surface of the peritoneum of the cul-de-sac was covered by plaques of tumor cells similar to those described in the liver. Bile was not seen in any of these cells. One large lymph node on section showed areas of lymphoid tissue replaced by sheets of liver-like epithelial cells as described in the tumor in the liver; none showed bile pigment. Many phagocytic cells were filled with both hemosiderin and thorotrast. Several smaller nodes from the omentum showed no tumor, but the lymphatics of the pericapsular tissue were dilated. Two sections of the lung showed discrete, round nodules of liver-like tumor as described in the liver with compression of the adjacent alveoli.

The anatomic diagnosis was carcinoma, liver. Carcinoma, metastatic, lymph nodes, retroperitoneal and peribronchial; carcinoma, metastatic, lungs; carcinoma, metastatic, peritoneum. Thrombosis, inferior vena cava. Thrombosis, veins, iliac, renal, adrenal, testicular, internal mammary; and transverse sinus. Embolism, pulmonary artery, multiple.

Comment. The clinical course of this patient during several months prior to his death was notable for (1) marked hypothermia and periodic generalized convulsions both of which were of unknown origin, (2) gradually increasing edema of the legs without signs at any time of ascites, (3) absence of jaundice, and (4) an unusually voracious appetite which caused the patient to eat unusually large quantities of food with enjoyment.

The hypothermia (figure 4) was striking. Readings of the temperature made rectally revealed in the period of observation 156 readings at 36° C. or less and 4 readings of 35° C. or less. The cause of this hypothermia is

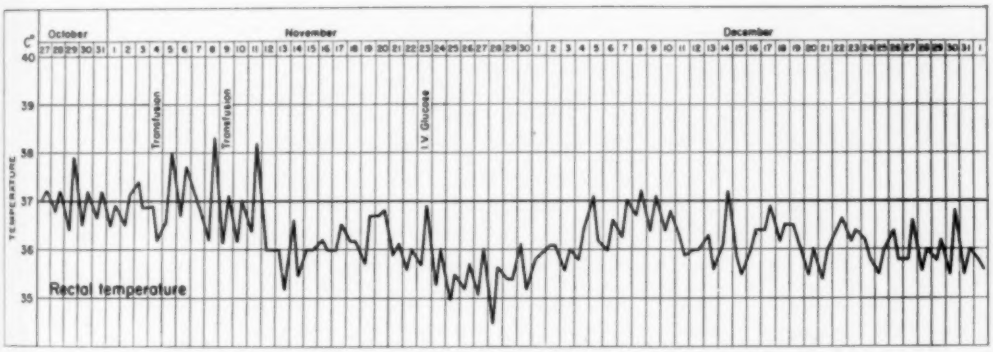


FIG. 4. Temperature chart showing marked hypothermia. (Case 1)

unexplained and so far as we are aware has not previously been reported in primary cancer of the liver, to which of course it may have no relation. This finding is in contrast to that of Mathews [15] who in reporting 16 cases of this disease noted that a septic temperature was not infrequent and in the absence of demonstrable hepatic tumor or enlargement a symptom which could easily be interpreted as that of an infectious disease.

Metastasis to the Heart. Metastasis to the heart is very unusual in primary carcinoma of the liver. Gregory [16] reported such a case and collected 11 others from the literature in which there was a tumor thrombus in the inferior vena cava and right auricle. The two uniformly occurring clinical findings in such cases were swelling of the lower extremities and of the abdomen. He concluded that "the occurrence of orthopnea, marked increase in venous pressure, sudden increase in edema of extremities and scrotum, and sudden increase in size and tenderness of liver in a patient who presents reasonable evidence of tumor thrombosis of inferior vena cava should be interpreted as good evidence that tumor thrombus has formed in the right auricle." In one of our cases there rapidly developed clinically

one month before death ascites, fluid in the right pleural cavity, and edema of the lower extremities and genitalia, associated with jaundice and a palpable mass in the right upper quadrant of the abdomen. At the time of postmortem examination in addition to primary carcinoma of the liver there was found extension of the tumor into the hepatic vein (figure 5) and inferior vena cava and one mass of tumor cells enmeshed in a thrombus attached to the tricuspid valve.

Pathologic Data

Primary carcinoma of the liver occurs in two main types, that arising from liver cells and that originating from intrahepatic bile ducts. In 1911 Yamagiwa [17] reintroduced the terms "hepatoma" and "cholangioma" to designate these two types, respectively. These terms which formerly had been originated by Sabourin [18] have since obtained rather widespread usage. Inasmuch, however, as they do not tell us specifically whether a given tumor is benign or malignant, except by implication, we prefer not to use them. For the sake of clarity, it might be better to speak specifically of liver cell carcinomata, and bile duct carcinomata. Should one wish to vary the terminology, it would also be acceptable to speak of primary carcinoma of the liver, of either hepatoma or cholangioma type as the case may be.

Even though 49 cases * of primary carcinoma of the liver constitute our series, in only 40 were the clinical data sufficient to warrant clinical analysis. The morphologic data, however, are quite complete. Hence, the following analysis and statistics are on the basis of 49 rather than 40 cases.

The essential pathologic data for the 49 cases are summarized in table 2.

Incidence of Primary Carcinoma of Liver in Relation to Total Cases of Carcinoma. Sixteen hundred thirty-two cases of primary carcinoma occurred in the 11,045 autopsies previously noted to be in the records of the Department of Pathology of the Stanford University School of Medicine. In other words 14.77 per cent of our necropsy material consisted of cases of primary carcinomata. Primary hepatic carcinoma constitutes 3.01 per cent of this group. Figures given in the literature on the ratio of primary liver carcinoma to all other carcinomata are quite variable and difficult of interpretation. Most of the recent statistical studies include malignant diseases of the gall-bladder and bile passages along with those of the liver. Various figures which one finds frequently quoted in the literature are those of Orth, Hansemann and Rindfleisch, 0.5 per cent cited by Ewing [19]; Jaffe [20] 1.5 to 3.0 per cent; Brines [21] 8.4 per cent and Smith [22] 17 per cent in the Philippine Islands.

Relation of Cirrhosis to Development of Primary Liver Carcinoma. Among Caucasians cirrhosis seems to be the chief predisposing factor, and

* Not included in the series are two older cases in which no microscopic studies were made (No. 116 and No. 171, January and November 1873); one in which histological slides are no longer available, previously diagnosed "Sarcoma" III-94; as well as a case in which only the microscopic postmortem record remains (V-149).

has been accepted quite universally as such by most authors. According to Ewing [19] cirrhosis is found in about 85 per cent of "hepatomata," and 50 per cent of biliary tumors. In our series cirrhosis * was found in 27 cases, an incidence of 54 per cent, which is considerably lower than the figures reported in most series. Even though an incidence of 54 per cent is pertinent, it is on the other hand sufficiently low to indicate that the two conditions may occur independently, and that they may occur coincidentally, without any direct causal relationship. It may be that the discrepancy in statistics can be explained on differences in the adequacies of diet (vitamin B, riboflavin). Certainly, the studies of Sugiura and Rhoads,[10] as well as those of Kinosita,[8] and Kensler and co-workers [9] would suggest the possibility that in patients with cirrhosis the development of hepatic carcinoma might be prevented if the diet were made rich in components of the vitamin B complex. In this regard, it should be noted that clinical cases of deficiency of vitamin

TABLE II

Primary Carcinoma of Liver

Anatomic Data in 49 Cases

	No. Cases	Per Cent of Cases
Sex		
Males	47	95.92
Females	2	4.08
Size of Liver		
Above average*	36	73.47
Average	8	16.33
Below average**	4	8.16
Size not stated	1	
Type of Tumor		
Liver cell carcinoma	45	91.8
Bile duct carcinoma (intrahepatic)	4	8.2
Thrombosis portal vein (extrahepatic)		
Thrombosed	7	14.3
Not thrombosed	20	40.8
No statement	22	
Ascites		
1,000 c.c. or more	28	57.1
Less than 1,000 c.c.	16	32.7
None	3	6.1
No statement	2	
Hemoperitoneum	12	24.5
Pigmentation liver	5	10.2
Hemochromatosis	3	6.1
Hemosiderosis liver	2	4.1
Giant cells	21	42.8
(not stated—8)		
Bile formation	17	34.7
(not stated—8)		

* In excess of 2,000 grams or 28 by 14 by 10 cm.
** Below 1,500 grams or 22 by 12 by 8 cm.

* In this group we have included only those cases to which we refer as primary cirrhosis. For the purpose of this paper cardiac and biliary forms are classed as "secondary" and are not computed. As is indicated in table 3, the statistical series comprises advanced portal (Laennec's) cirrhosis, active early and subacute stages, and "limited" cirrhosis. By the latter term we refer to those cases in which the disease was limited in extent, not accompanied by ascites, and not associated with a clinical symptom complex. In all cases the diagnosis was made and confirmed microscopically.

B complex of marked degree are uncommon in San Francisco as compared to some other parts of the country.

Incidence of Cirrhosis in Total Necropsy Series. The incidence of cirrhosis, in the total necropsy series of 11,045, is 4.22 per cent. If only the advanced forms are considered, the incidence drops to 3.13 per cent. This is practically the same incidence as reported by Loesch [12] in a smaller series in which he found 94 cases of advanced cirrhosis in 3,000 autopsies—3.13 per cent. He noted that 12.5 per cent of such cases developed carcinoma, and that 12 of his 14 cases of liver carcinoma or 85.7 per cent had cirrhosis. In our series 14.2 per cent of cases with advanced cirrhosis presented carcinoma of the liver. Because of the implication that cirrhosis is a predisposing factor in the pathogenesis of cancer of the liver, however, it may be preferable to calculate the ratio between cirrhosis and cancer on the total cases of cirrhosis rather than those which are solely in the advanced group. When calculated for the total cases of cirrhosis the incidence drops to 10.5 per cent.

We have noted a striking increase in the incidence of advanced portal cirrhosis in the post-prohibition era. It has been possible conveniently to divide the cases into three groups, roughly corresponding to the pre-prohibition, prohibition and post-prohibition eras. Several startling figures are apparent in the analysis of these data and are presented in table 3.

TABLE III

Relation of Cirrhosis to Carcinoma of Liver

Year	Number Autopsies	Advanced Cirrhosis	Early and Subacute Cirrh.	Limited Cirrhosis	Total Cases	Carcinoma Liver	% Carcinoma in Cirrhosis
1898–1923	3000	*69*	2	60	131	15	11.5%
1923–1934	3661	*91*	22	22	135	15	11.1%
1934–1942	4384	*186*	9	15	210	19	9.0%
Total	11,045	346	33	97	466	49	10.5%

In the post-prohibition era cases of advanced cirrhosis have increased 104 per cent (from 91 to 186) in contrast to a series the size of which is only 19.2 per cent larger (4,384 in contrast to 3,661) than that in the prohibition era. When the figures are broken into these three groups, it will be noted that even though there has been a remarkable increase in the incidence of portal cirrhosis there has not been a corresponding increase in incidence of primary carcinoma of the liver. It is further to be noted that there has been a slight drop in the actual incidence of carcinoma among the total cases of cirrhosis, namely, from 11.1 per cent to 9.0 per cent, the cause of which is not clear.

In studying each of our cases we are impressed by the fact that the antecedence of nodular hypertrophy is not a uniform occurrence in those cases of cirrhosis which developed carcinoma. Even though such hypertrophy is present in some cases it apparently does not constitute an essential

part of the "preliminary picture." The existence of marked nodular hypertrophy of the liver does not in itself act as a precursor for cancer, as is illustrated by the following case in which extensive nodular hypertrophy was known to exist 11 years previously. The difficulty of histological diagnosis of primary carcinoma of the liver is apparent in this case also.

*Case 2.** (GG–509) (not included in tabulations). The patient, a woman aged 34 years, came under observation four and a half months prior to exploratory laparotomy because of painless jaundice without fever. The liver was large. Ascites was absent. Eighteen pounds in weight had been lost. Wassermann and Kahn test reactions were negative. At operation, April 23, 1931, the liver was found to be markedly enlarged. The right lobe of the liver was level with the umbilicus and the anterior superior spine of the ilium. Throughout the liver were numerous, firm, slightly dark areas, varying in size from 0.3 to 3.0 cm. Those near the surface were raised and appeared to be scattered diffusely throughout both lobes. The extrahepatic biliary passages were explored and found to be essentially normal. Lymph nodes at the hilus were enlarged. The spleen was small and firm. One lymph node and a piece of the liver were removed for histological study and diagnosis.

A diagnosis of "Carcinoma of liver, primary" was made by Dr. William Ophuls. Sections were sent to Dr. James Ewing at Memorial Hospital in New York City, who made the following comment: "The sections . . . are somewhat difficult to interpret. The case impresses me as one of primary toxic liver necrosis followed by regeneration of liver tissue. The regeneration is excessive and takes the form of low grade, almost adenomatous hyperplasia. I do not think it is a true primary malignant neoplasm." Dr. Ophuls reviewed the sections offering the following comment: "When I first saw the sections, I thought of the possibility of an excessive regenerative proliferation in an acute cirrhosis. The proliferating liver cells were so atypical in their appearance and arrangement that I concluded that there was present a malignant change. In this I was supported by the description of the gross findings. I may be in error, but I am not convinced of it after a renewed study of the specimens. You would do me a great favor if you should let me know future developments in this case."

The fact this patient is alive and well in 1942 almost certainly disproves the diagnosis of carcinoma which was made 11 years previously. It emphasizes the difficulties of diagnosis, the need for careful follow-up in all such cases in which the diagnosis is made from surgical biopsy, and shows that the possibility of regenerative hyperplasia must be excluded before any case in which a diagnosis of carcinoma of the liver is made can be accepted as cured. The above case is also of interest in that the patient is perfectly well and at present has neither signs nor symptoms referable to disease of the liver.

Age. Primary carcinoma of the liver occurred at ages from three months to 77 years. Most of the cases were found between the ages of 41 and 70 years. However, it is notable that nine of them occurred before the age of 40 years. Aside from five cases occurring between 71 and 77 years, the rest were fairly well distributed in the three decades between 41 and 70 years.

* Through the courtesy of Dr. L. R. Chandler, San Francisco, California.

Sex. Ninety-six per cent of our cases occurred in males. The predominance of the disease in males has been quite generally observed by others. In our series, however, the preponderance of males is unusually marked.

Race. Sixty-seven per cent were in people belonging to Caucasian stock. The remainder occurred in races which comprise but a small proportionate part of the local population. We are impressed by the fact that 19 per cent of our cases occurred in Chinese. The distribution according to race is as follows:

Oriental		11
Chinese	9	
Japanese	2	
Ethiopian		3
Native American	2	
Abyssinian	1	
Malayan		2
Filipino	1	
Native Guam	1	
Caucasian		33
French	4	
Italian	2	
Greek	2	
Russian	1	
Miscellaneous	24	

Size of Liver. Approximately three-fourths of the livers were larger than normal. Thirty-six or 73.5 per cent of them weighed in excess of 2,000 grams or measured more than 28 by 14 by 10 cm. In four of the cases the liver was smaller than normal, and in each of these advanced portal cirrhosis was present.

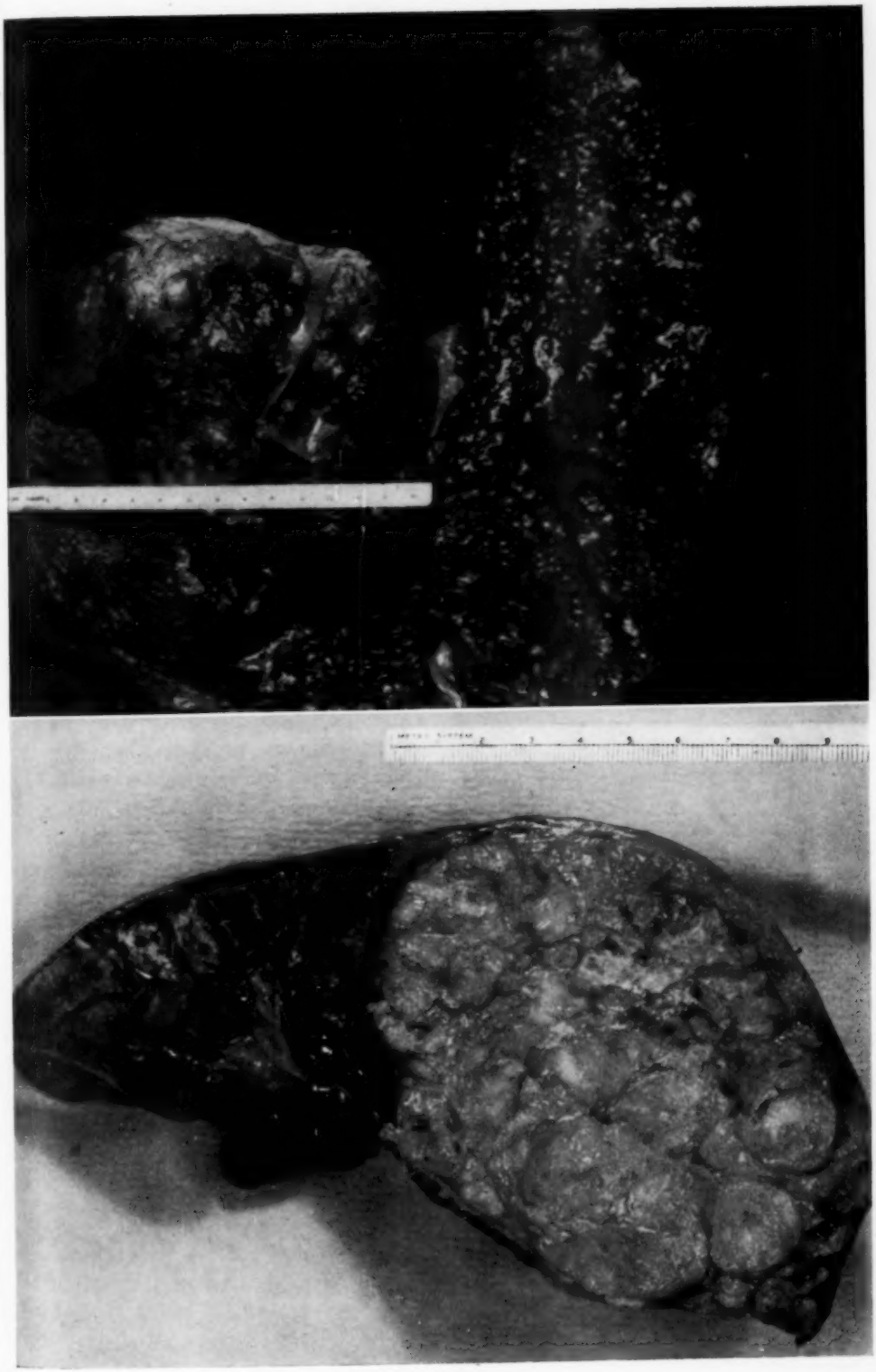
Ascites. Forty-four cases were accompanied by ascites. In two no statement was made referable to peritoneal fluid, and in three it was definitely stated that fluid was not present.

Thrombosis of Portal Vein. Specific statements referable to the status of the extrahepatic portal vein were not uniform and were frequently omitted in the autopsy records. The vein was definitely thrombosed in seven instances. In 20 instances no thrombosis existed, and in 22 no statement was made.

Hemoperitoneum. Frankly bloody fluid was present in 24.5 per cent of the cases. In nine of the 12 cases the amount was in excess of 1,000 c.c. As much as 3,000 c.c. were present in each of two cases. In all cases the bleeding was due to rupture or laceration of Glisson's capsule overlying tumor nodules. It is evident that hemoperitoneum must be considered as one of the important causes of immediate death in these cases. A number of individual case reports in the literature report hemoperitoneum as the mode of exitus.

FIG. 5. Moderately enlarged, diffusely nodular liver as viewed from posterior aspect. A large subcapsular tumor is faintly discernible at the dome of the right lobe. Note the extension of tumor into the hepatic vein. The nodular, hob-nailed appearance is due to both cirrhosis and tumor.

FIG. 6. Transverse section of liver (weight 780 grams), showing primary tumor in left lobe. (Case 3.) (× 3/4)



FIGS. 5–6.

Type of Tumor. Ninety-two per cent of the tumors were primary liver cell carcinomata. Only four cases appeared to originate from bile ducts. In one case the origin of the primary lesion was difficult to interpret. Metastases from it, however, showed the typical structure of liver cell carcinoma.

Bile formation was noted in 35 per cent and giant cells in variable numbers were found in 43 per cent of the cases. Both of these histological features were found only in cases of liver cell carcinomata. Storage of fat was frequently noted. In none of the five cases of disturbed pigment metabolism was iron pigment found in the tumor cells.

Hemochromatosis. In 11,045 autopsies hemochromatosis occurred 20 times. In our series there are five cases of hepatic pigmentation, three of which are considered as cases of hemochromatosis and two as of hemosiderosis. In none of the five cases are tumor cells laden with iron pigment. Three of the cases of hemochromatosis were associated with the development of primary liver cell carcinoma, an incidence slightly higher than for the total group of cases of cirrhosis, namely, 15 per cent as compared with 10.5 per cent (table 5). Various authors have correlated the occurrence of primary cancer in hemochromatosis with divergent conclusions, some of which are discussed in this paper in the section following the report of a case of hemochromatosis (case 4).

Other Neoplasms Present. Two of the 49 cases were associated with the presence of other neoplasms, and in neither case did there seem to be any doubt as to the nature of the tumors, for in one of them there was a coincidental encapsulated small "hypernephroma" of the left kidney (No. 17, 19–21) and in the other a small scirrhous carcinoma of the breast (No. 21, 36–274).

Metastases. Without wishing to enter too deeply into the argument whether cancer of the liver is unicentric or multicentric in origin, we considered that intrahepatic metastases had occurred in 44 of our cases (90 per cent). The following points influenced us in deciding that the multiple tumors in the liver were on the basis of intrahepatic metastasis rather than on that of multicentricity of origin: (1) the marked affinity of malignant liver cells for the liver (as based upon the large number of intrahepatic masses), (2) the infrequent extrahepatic metastases, (3) the non-uniformity in the distribution of intrahepatic tumors, and (4) the frequency with which portal venules and lymphatics were permeated.

Extrahepatic metastases generally were infrequent. This is striking in view of the large number of cases in which the hepatic veins were plugged with tumor thrombi, parts of which frequently extended into the inferior vena cava and even into the heart. The contrast between the multiplicity of lesions in the liver and the sparsity of extrahepatic metastases suggests that neoplastic liver cells are so "individualized" they grow best in the liver, and find it difficult to adapt themselves to other tissues. Certainly, with tu-

morous thrombi from the hepatic vein (figure 5) in intimate contact with the circulating blood, cast off tumor cells must find their way frequently to other organs. Only 26 cases of extrahepatic metastases were found. Twelve of these were in the lungs.

It is also to be noted that lymph node metastases were found in only 18 cases. In a few cases several sets of lymph nodes were involved, for example, the mediastinal or cervical nodes in addition to the regional nodes at the hilus of the liver. Data referable to metastases are summarized in table 4.

TABLE IV

Metastases in Primary Carcinoma of Liver

	Organs in which metastases were found									
Total cases primary:	liver	lungs	peritoneum	bones	adrenals	pleura	stomach	spleen	heart	soft, paraverteb. tissues, back
49	44	12	5	2	2	1	1	1	1	1

*Metastatic Index**
Including liver 1.43
Excluding liver 0.53

Lymph Node Metastases: (Number of cases in which following groups of lymph nodes were involved).
Regional (hilar, portal, abdominal) 14
Retroperitoneal 3
Mediastinal 2
Cervical 1

* Metastatic index, average number of sites of metastases per fatal case (See Page 9, Cancer Handbook, Liljencrantz, Stanford Univ. Press, 1939).

In the majority of cases in which multiple tumor nodules were present in the liver, there were found dilated lymph vessels in the periportal regions, and not infrequently engorgement of the small radicals of the portal and hepatic veins. Permeation of such vessels may be present in the apparently early stages of the disease for in one of our cases appearing in the files as one of "Multiple Adenoma of the Liver" review of the sections reveals periportal lymph vessels permeated with tumor.

Report of Two Cases of Unusual Pathologic Interest. In this series there were two cases which we feel were of such unusual interest as to warrant separate consideration. The first is that of an infant in whom an abdominal mass was palpated three days after birth. Not only because of the histologic structure of the primary lesion, but because of a metastasis in the humerus we feel beyond all doubt that this is a case of neo-natal malignant epithelial tumor. Undoubtedly, the carcinoma developed in utero in a mother who was and has continued to remain in apparent good health.

This case is the youngest of primary liver carcinoma encountered in our experience and noted by us in the literature.

Case 3 (OD–99). A male infant aged three days was admitted to the hospital because of icterus and a prominent abdomen which on examination proved to be due to a large mass occupying the region of the left lobe of the liver. Laboratory studies revealed the number of erythrocytes to be 6,010,000 per cubic mm.; hemoglobin was 110 per cent (Sahli), the icterus index 64, the Van den Bergh reaction indirect, and the value for serum bilirubin was 18.5 units. Roentgenologic examination of the gastrointestinal tract showed an extensive tumor that displaced the colon and stomach downward.

One month later the mass was found to be distinctly larger but freely movable and several large superficial veins were present over the surface of the upper abdominal wall. At this time surgical exploration revealed an enlarged left lobe of the liver but a definite tumor mass could not be observed.

Two months later flaccid paralysis of the left arm was discovered and roentgenologic studies showed an area of irregular bone destruction with increase in density at the proximal end of the humerus. There was gradual failure and death occurred at the age of 15 weeks. The clinical diagnosis was tumor of the liver, probably carcinoma with pathological fracture of the left humerus.

At the time of postmortem examination the infant was found to be well developed and the weight was 4,450 grams. The liver was markedly enlarged (780 grams). The right quadrate and caudate lobes appeared normal, whereas the left lobe was very large and measured 9 by 12 by 14 centimeters (figure 6). The capsular surface was irregularly nodular, firm, and on cut section a few soft necrotic spots were observed in the large tumor mass. The extrahepatic biliary passages were patent throughout and the portal venous system was unobstructed. The gall-bladder appeared normal. There was slight fullness of the upper third of the left humerus.

Microscopic sections of intact liver parenchyma revealed normal sinusoidal architecture and liver cells (figure 7). One section contiguous with the tumor showed large areas of fibrous tissue supporting numerous small bile ducts, but devoid of liver cells as well as tumor cells except for occasional dilated lymph vessels engorged with them (figure 8). Sections of the tumor disclosed cells varying in appearance from those closely resembling liver cells and forming lobule-like masses separated by capillaries and fine septa of delicate fibrous tissue to other areas in which they formed cords of cells with tubular forms resembling bile ducts. The tumor cells generally presented cytoplasm which was pale and granular and occasionally contained small droplets of fat. Mitotic figures were present but not numerous. Areas of necrosis were not uncommon.

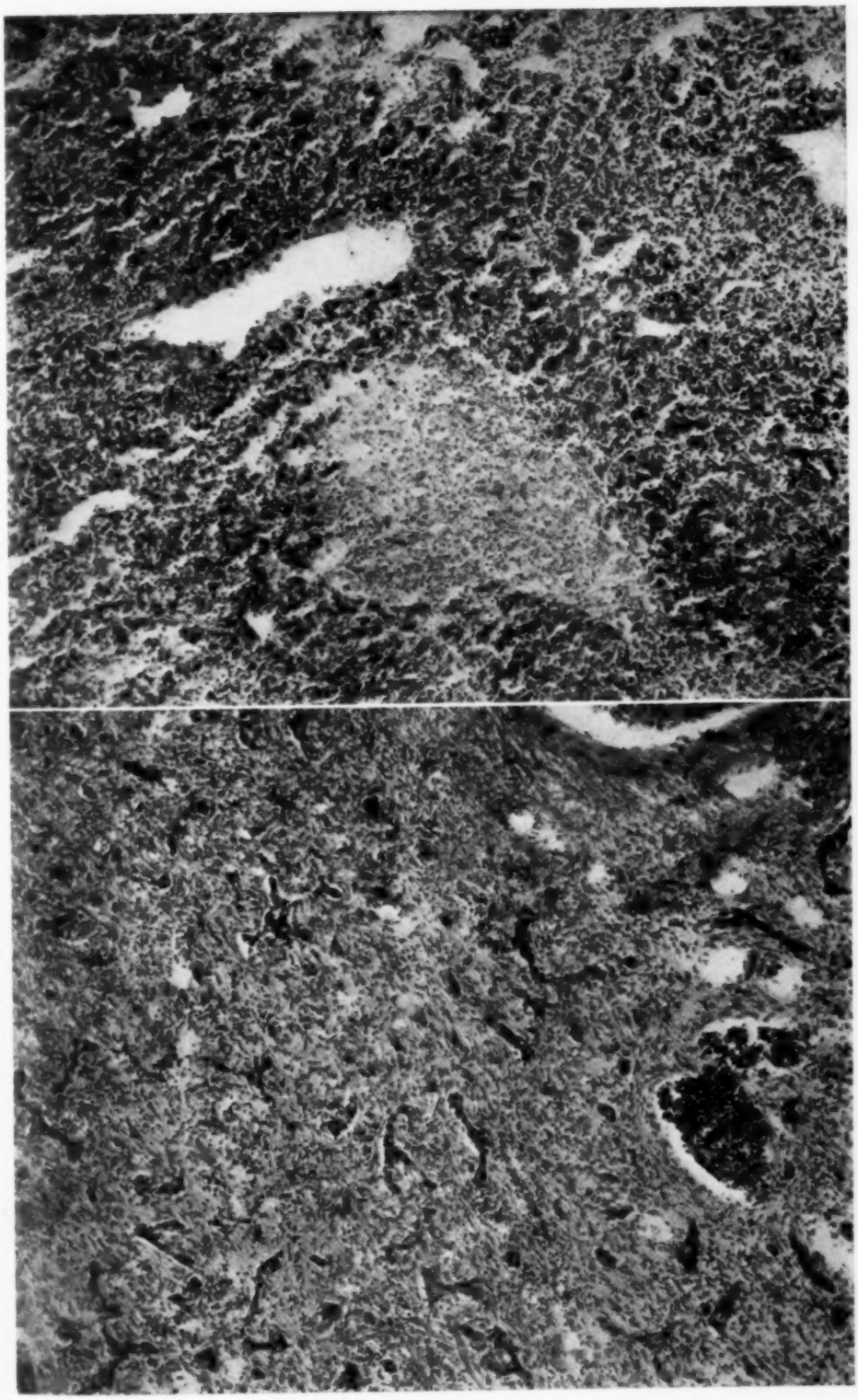
Sections of the humerus presented large areas of tumor, the cells and structure of which resembled those of the tumor in the liver (figure 9).

The anatomic diagnosis was carcinoma of the liver with metastasis to the left humerus, bronchopneumonia, subacute ulcer of the duodenum, and mild reticulum cell hyperplasia of the spleen.

Comment. Not only the primary tumor but the intrahepatic metastases were limited to the left lobe. A possible anatomical explanation for this

FIG. 7. Carcinoma of liver surrounding an island of preëxistent liver tissue whose cells are pale and laden with lipoid. Note the lobular structure of the tumor and its tendency to grow in cords supported by a delicate fibrous frame with intervening vascular spaces. (Case 3.) (× 100)

FIG. 8. Area devoid of liver cells. Note relative increase in bile ducts and the abundant fibrous tissue stroma. Is this the result of an old, intrauterine toxic necrosis, or does it represent agenesia? Two lymph spaces are engorged with tumor cells. (Case 3.) (× 200)



FIGS. 7–8.

localization is one advanced by McIndoe and Counseller [23] who by means of injections demonstrated that the liver is in a sense a symmetrical organ, with right and left lobes possessing distinct vascular supply and biliary drainage. In their studies the line of demarcation extended from the gall-bladder fossa to the point of entrance of the hepatic veins into the inferior vena cava. Both Helvestine [24] and Lee [25] have shown that the lymphatics lie along the distribution of portal spaces and hepatic veins, and that the flow is efferent

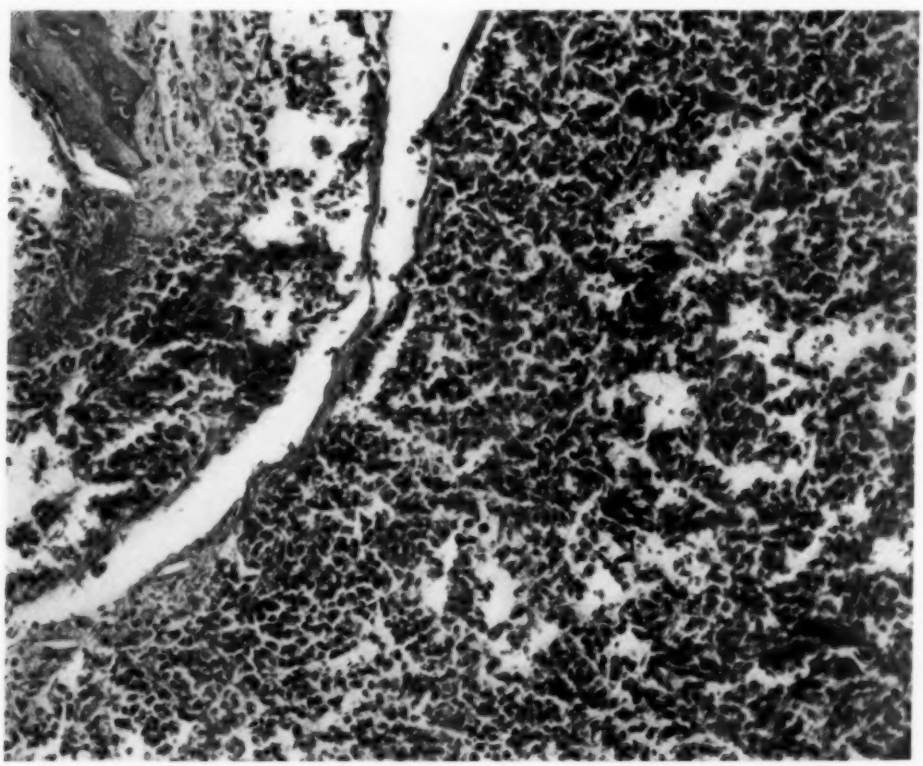


FIG. 9. Humerus. Metastatic tumor possesses a structure similar to that of the primary tumor seen in figure 11. A bone spicule is present in the upper left hand corner. (Case 3.) (× 200)

in both cases. On anatomical grounds then it is not surprising that no metastatic tumors were found in the right lobe. Possibly the relatively short duration of the disease accounts for the absence of recognizable metastases in the right lobe, whose cells of origin could have reached there through the systemic circulation after having passed through the pulmonary and portal capillary beds. The extrahepatic metastasis in the humerus was almost certainly hematogenous in origin. Although it cannot be definitely proved, it is most likely that the inception of this tumor was during the fetal life of the infant. No giant cell syncytial masses nor bile production were noted.

The areas of fibrous tissue seen in figure 6, where liver cells are absent but small bile ducts numerous, present an appearance not unlike that seen following toxic necrosis. The possibility of an agenesia cannot be excluded. However, the existence of such areas suggests that during pregnancy the mother may have sustained an unrecognized toxic necrosis with concurrent changes in the fetal liver. There is no history of administration to the mother of hepatotoxic drugs during the pregnancy. It is noteworthy that the mother has been and continues to appear healthy.

It is quite generally recognized that in spite of various reported series of cases primary cancer of the liver is rare in children. A comprehensive study of the incidence of it in children was made by Steiner [26] in 1938. He reported two cases of his own. Out of 105 cases occurring under 16 years which he collected from the literature he felt that only 65 could be accepted as primary carcinomata. Steiner [26] pointed out that secondary growths are found much less frequently in children than in adults. Greene [1] has pointed out that cirrhosis is found much less commonly in the primary carcinoma of children than of adults. Interesting case reports since the review of Steiner [26] are those of Wentz and Kato,[27] Hansen et al.,[28] and Osterlin.[29] The case of Wentz and Kato is that of a liver cell carcinoma in a girl of six years with progressive splenomegaly, anemia, and leukopenia of three and one-half years' duration. There ensued severe gastric hemorrhages, terminal jaundice and ascites. This is the first reported case in children in which it is reported that the neoplasm was associated with Banti's syndrome. The case reported by Hansen and co-workers [28] was that of a boy of 10 years who exhibited lipemia of marked degree and pronounced osteoporosis of the entire skeleton. The carcinoma was of the liver cell type and had given rise to metastases in the lung and spleen. There was associated with it lipid histiocytosis of the spleen, liver, lungs, right kidney and bone marrow along with an extreme atrophy of the bones with spontaneous fractures of the ribs. It is of passing interest to note that the tumor cells not only stored fat but were bile producing. The case of Osterlin [29] was that of a male infant of 10 months, whose clinical course was uneventful until five months of age. There then developed two bouts of diarrhea followed by gradually developing constipation, and two weeks prior to hospital entry discovery of a tumor in the abdomen. The child died two and a half months later at the age of 12 and one-half months. Autopsy revealed multiple tumors in the liver, the largest of which was in the right lobe and measured 15 by 9 centimeters. Microscopically it was of the liver cell type. Many of the tumor cells were laden with lipoid. Marked fibrosis existed about the neoplastic areas.

The extreme rarity of pre-natal malignant epithelial growths has been clearly brought to our attention by Wells.[30]

Primary Carcinoma of the Liver in Hemochromatosis.

Case 4 (8C–148). The patient, a man aged 60 years, developed three years prior to his death glycosuria, hyperglycemia and pigmentation of the skin so that a diagnosis of hemochromatosis was made. The liver was not enlarged at that time. One

FIG. 10. Multiple small non-pigmented yellowish white tumor nodules scattered throughout main lobe of liver, and brought into relief against a pale chocolate brown background. The hepatic vein is widely dilated and engorged with tumor. (Case 4.) (× ½)

year later the liver was found to be enormously enlarged although pigmentation of the skin and glycosuria remained essentially unchanged. Two months prior to his death the patient entered the hospital because of pain in the right upper quadrant of the abdomen. The skin was definitely bronzed, the liver large and tender. The

fasting value for blood sugar was 124 milligrams per cent, the icterus index was 10 units, and glycosuria was absent. There was gradual failure with death from bronchopneumonia.

At the time of postmortem examination there was dark bronze pigmentation of the skin most intense about the neck, malar prominences, backs of the hands and wrists and over the feet and legs. Five hundred cubic centimeters of thin straw colored fluid were contained in the peritoneal cavity. There was marked enlargement of the liver which weighed 4,480 grams and measured 39 by 30 by 13 centimeters. The

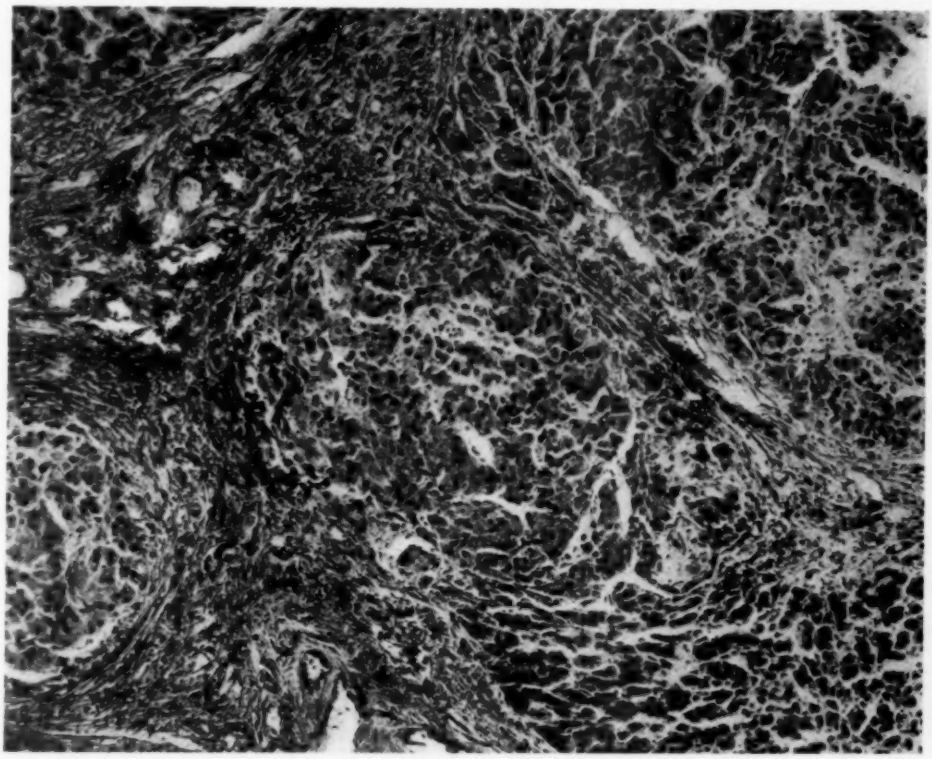


FIG. 11. Nodules of liver cell cancer separated by strands of fibrous tissue with a few imprisoned small pigment laden residual liver cells. The tumor cells are non-pigmented. The section is stained for iron by "Prussian Blue" technic. In the upper left hand corner, and in the lower right hand corner the parenchymal liver cells are dark and prominent—their cytoplasm being heavily laden with pigment. (Case 4.) (× 100)

surface of the right lobe was studded with numerous small, soft, yellowish nodules which upon cut section were found to be densely grouped into fan-like masses extending from the hilus of the liver to its anterior surface. These nodules were most dense in a zone 8.5 centimeters in width on either side of which the nodules became less numerous and more scattered in distribution. The nodules decreased abruptly in number at the line of demarcation between the right and left lobes, and only a few widely scattered and isolated nodules measuring up to 0.5 centimeter were present in the left lobe (figure 10). The parenchyma of the liver cut with a slight increase in resistance, was slightly rubbery, distinctly pigmented, and finely lobulated by narrow, slightly depressed strands of fibrous tissue (figure 11). The right intrahepatic

branch of the portal vein and its major radicals were filled with tumor and thrombus. The extrahepatic portal vein was patent. The spleen weighed 500 grams and was pigmented. Prominent submucosal varices were present in the lower third of the esophagus.

Retroperitoneal lymph nodes were moderately enlarged, soft and pigmented but did not present evidence of gross tumor. The adrenals were normal in size with cortices grossly depleted in lipoid and somewhat narrowed. The medullae were dark brown.

Histologic study. Studies of sections of the liver revealed the parenchyma to be divided into a number of irregular islands and separated by narrow bands of fibrous tissue. Liver cells and reticuloendothelial cells contained finely granular yellowish-brown pigment (chiefly hemosiderin). The tumor was composed of large cuboidal to polygonal cells arranged in slightly irregular cords and the tendency toward reproduction of hepatic lobules was quite pronounced (figure 11). Occasional multinucleated giant cells were observed. Bile pigment was present in many areas and stains with Prussian blue were striking in that the tumor cells were free of iron containing pigment except for an occasional widely scattered cell which contained it.

Studies of the sections of the endocrine glands revealed striking deposits of pigment. The cortex of the adrenals was about one-half normal width and its cells laden with rather large amounts of brown granular pigment. Moderate amounts of the pigment were deposited in the pars anterior of the pituitary, less in the pars intermedia and none in the pars nervosa. The cells of the parathyroid glands showed the majority of chief cells heavily laden with iron containing pigment. There was much increase in adipose tissue and some in fibrous tissue in the pancreas. Islets of Langerhans were very infrequent. Much iron-containing pigment was found in the fibrous tissue or within the cytoplasm of the acinar and islet cells.

The anatomic diagnosis was hemochromatosis (liver, pancreas, adrenals, thyroid, parathyroids, testes, spleen; cirrhosis of pigment variety; atrophy of adrenals, hypophysis, parathyroids, thyroid, testis); persistence of thymus; ascites; esophageal varices; splenomegaly; carcinoma of the liver, primary liver cell type; carcinoma, metastatic, lungs, and bronchopneumonia.

Comment. Not only is this case of interest because of the development of primary liver cell carcinoma in the presence of hemochromatosis, but also because of the distribution of the metastases, all of which were intrahepatic except for a few in the lungs. The intrahepatic metastases were situated almost exclusively in the right lobe and decreased quite abruptly in number at the line of demarcation between the right and left lobes. This striking difference in distribution of intrahepatic nodules speaks for a spread in the right lobe on the basis of lymphatic permeation and tumor thrombosis of the portal venules. Thrombosis of the right portal vein indicates that retrograde thrombosis probably had occurred, thus enhancing the chance for distribution of satellite metastases in small clusters throughout the right lobe. The presence of occasional small nodules in the left lobe suggests that the cells of origin probably reached this site by way of the circuitous route through the pulmonary capillary bed and the hepatic artery, or even through the systemic and portal circulations. In spite of the rather uniform size of the nodules in the right lobe the evidence here favors a unicentric origin of them. Otherwise, in the presence of hemochromatosis and cirrhosis one would expect the tumor nodules to be more diffusely scattered throughout

both lobes. In this case pigmentation of the liver was a much more striking feature than cirrhosis which was only moderately advanced.

The relationship of hemochromatosis to primary carcinoma of the liver still is not clearly established. Rowen and Mallory [11] in 1926 reported a case of multinucleated liver cell carcinoma and cited, in the records of the Boston City Hospital, three additional cases of hemochromatosis with primary carcinoma of the liver. They expressed the opinion that "the pigment type of cirrhosis, which requires probably the longest time for its production, some 10 to 25 or more years, seems to be the variety" (of cirrhosis) "most commonly associated with liver cell cancer." They conclude, "judging from these examples and others in the literature, pigment cirrhosis is the type which is most commonly complicated by liver cell carcinoma."

Binford, Lawrence and Wollenweber [31] in 1938 reported an additional case and reviewed the literature up to that time. They cited the monograph of Sheldon [32] in which there is reviewed the status of hemochromatosis in British Hospitals. Sheldon had collected 363 accepted cases of hemochromatosis. Among these there were 26 cases of primary carcinoma of the liver (7.1 per cent). Stewart,[33] another English author, found an incidence of 7.1 per cent of primary cancer in 124 cases of cirrhosis (after eliminating those in which slighter grades existed). Such closely similar percentages in cirrhosis and in hemochromatosis led to the conclusion that the cirrhosis rather than the pigmentation was responsible for the malignant changes of the liver found in hemochromatosis. In concurrence with our own observations, Sheldon [32] observed that the "most significant histologic feature was the absence of pigment from the malignant cells. These contained hemosiderin in only two cases." In the case reported by Binford et al.[31] small amounts of "hemosiderin" were demonstrated in not only some of the primary but also the metastatic tumor cells.

Failure of liver cells involved in areas of nodular hyperplasia to become pigmented in contrast to the rest of the liver is noted in a case (9C–246) in our records of hemochromatosis in which malignant changes were not present. A short résumé of the case is presented herewith.

Non-Pigmentation of Areas of Nodular Hyperplasia in Hemochromatosis.

Case 5 (9C–246) (not included in the tabulation). A man aged 60 years, a long standing alcoholic, entered the hospital with hyperplasia and hemiplegia from which he died. At the time of postmortem examination the liver was found to be slightly enlarged (2,200 grams), firm, slightly nodular and on cut section the texture of it was coarse brownish-red, and many small white nodules one to two centimeters in diameter were visible. Microscopic examination of liver tissue revealed a distinct increase in periportal connective tissue heavily infiltrated with lymphocytes in some areas. Most of the liver cells contained large quantities of dark brown granular pigment, but in the cells composing small poorly defined nodules of hyperplastic liver tissue the cells were large and contained only very small amounts of iron containing pigment. Many of the cells in these nodules contained large fat vacuoles.

This failure of benign and malignant hyperplastic liver cells to become pigmented is striking in view of the frequency with which the malignant tumor cells are shown to store fat and to form bile.

Discussion

Primary carcinoma of the liver presents many puzzling problems to the clinician and pathologist. For the clinician the disease remains one difficult of diagnosis without direct inspection of the liver at operation or by peritoneoscopy or until very late in the disease, when a large, irregular, nodular liver is found to be associated with jaundice and ascites in a patient without other signs of primary malignant neoplasm. This is not surprising when it is recalled that the liver is a large, relatively insensitive organ unless its capsule or its ducts suddenly are stretched, and that because of its great reserve capacity much of the liver may gradually be destroyed without production of appreciable symptoms or striking changes in tests for liver function.

Our experience in studying this group of cases, some of which we observed clinically, leads us to believe that the diagnosis should be suspected more often than it is, even though it may not be possible in many cases definitely to establish the clinical diagnosis. In considering the diagnosis the following factors seem worthy of mention. The marked preponderance of the disease in the male sex (96 per cent), its frequent occurrence before the age of 40 years (19 per cent), and the most commonly observed clinical findings of an enlarged and often nodular abdominal mass obviously the liver, fairly constant mild or moderately severe upper abdominal pain or discomfort, ascites, jaundice of mild or moderate degree, and absence of much indigestion. If a patient presented these clinical findings the natural suspicion would be that disease of the liver was present. Lack of roentgenologic evidence of intrinsic disease in the gastrointestinal tract, failure of the gallbladder to visualize following administration of suitable iodine-containing dyes, gradual increasing size, irregularity and nodularity of the liver, recovery of bloody ascitic fluid, and a rapid decline in health would all tend to strengthen belief in the diagnosis of primary carcinoma of the liver although they would not establish it. The frequency with which death may occur with bleeding into the peritoneal cavity from a carcinomatous nodule on the surface of the liver is striking in our series of cases.

Direct proof of the clinical diagnosis of primary carcinoma of the liver depends on inspection of the liver during an operation or peritoneoscopy with examination of tissue recovered for biopsy, or by direct puncture of the liver and examination of the tissue recovered in this way. However, studies of biopsy material may lead to confusing results as indicated in case 2 reported in this paper. Surgical exploration hardly seems justified as a diagnostic procedure and therapeutically it offers nothing in primary car-

cinoma of the liver or in those diseases most apt to be confused with it, such as cirrhosis of the liver.

Those clinicians who believe in the value of peritoneoscopy as a diagnostic procedure will be apt to believe that this method of examination could greatly aid in the diagnosis of carcinoma of the liver. Puncture of the liver without direct observation of it seems undesirable as a diagnostic procedure in cases suspected of primary carcinoma of the liver.

Consideration of the clinical data in our cases in terms of the type of tumor present in the liver failed to give us information which we could correlate to the extent of establishing clinical criteria for the diagnosis of any particular type of carcinoma of the liver, or the extent of involvement of the liver other than in determination of its large size.

In view of the several reported cases [28, 34] of associated xanthomatosis in children with primary carcinoma of the liver, it is noteworthy that neither this phenomenon nor lipemia was noted or recorded in any of our cases. In none of our cases was the disease characterized by changes associated with the so-called Banti's syndrome such as in the case reported by Wentz and Kato.[27]

The etiology of the disease remains a mystery. Cirrhosis was noted most frequently as a contributing factor or co-existent condition. The frequency with which primary carcinoma occurred in association with an otherwise diseased liver is striking (54 per cent), as is also the fact that in our experience it occurred less often in association with cirrhosis of the liver than has been reported by other observers (80 to 90 per cent of cases reported in the literature). Ninety-two per cent of the cases in our series were primary liver cell carcinomata, the type associated with a high incidence of cirrhosis. This might indicate that the two processes may be quite independent.

We have no evidence to offer on the possible relationship of deficiencies of components of the vitamin B complex to the development of this disease. Mention is made of it here because of the striking effects of yeast and other substances containing the vitamin B complex in inhibiting the development of primary carcinoma in the liver otherwise induced in the rat by a carcinogenic substance such as "butter-yellow." Clinicians should give attention to this problem not only in relation to cirrhosis of the liver but in particular to all conditions which result in diffuse disease of it.

In the cases of hemochromatosis we were impressed by the fact that not only the tumor cells in those cases with primary carcinoma of the liver but also the hyperplastic liver cells in a case of nodular hyperplasia (case 5) failed to store demonstrable amounts of iron containing pigment. In contrast to numerous cases in which tumor cells were seen to produce bile and to store fat, the failure to deposit this pigment seemed to represent a possible defect in the metabolism not only of the neoplastic liver cells but of the hyperplastic liver cells as well.

In our experience based upon postmortem records, cases of portal (Laennec's) cirrhosis have doubled since prohibition was repealed in 1933. Yet the incidence of cancer of the liver in cases of cirrhosis has slightly decreased.

Parasitic infestation is almost completely excluded as an etiologic factor. In only one case were parasites actually demonstrated (*Ascaris lumbricoides*). In none of our cases was infestation by liver flukes or by any of the species of schistosoma present. The mechanism of cancer production and its high

TABLE V

Case No.	Age	Type of Pigmentation	Cirrhosis	Size Liver	Bile	Fat Storage
8C–148	60	Hemochromatosis	+	4,800 gm.	+	+
9C– 94	72	Hemochromatosis	+	1,800 gm.	+	
21– 17	50	Hemochromatosis	+	34×26×14	+	+
33–186	73	Hemosiderosis	+	27×12× 7	−	
23– 33	60	Hemosiderosis	+	19×14× 8	+	

incidence among races infested with schistosomiasis is not clear. Even in tropical countries in which most people dying from cancer of the liver show parasitic infestation, it would seem that in view of the high incidence of parasitic infestation throughout the population such infestation is not a significant etiologic factor in the production of primary carcinoma of the liver.

The incidence of primary carcinoma of the liver in autopsy statistics of the Department of Pathology of the Stanford University School of Medicine in San Francisco is 0.444 per cent, an incidence somewhat comparable to other localities in the United States. It is significant that 19 per cent of these cases occurred in Chinese.

Carcinoma of the liver constituted 3.01 per cent of our carcinoma deaths. (Malignancies of types other than carcinoma are excluded from this compilation.) Strictly comparable figures are not readily available inasmuch as most statistics of carcinoma of the liver include tumors of the gall-bladder and bile ducts. In all but one of our cases the diagnosis of malignancy was readily made. The exception was a case of multiple tumors in which the original diagnosis of "Adenoma" is disproved by the discovery of occasional lymphatic channels permeated with tumor. A clinical case of primary toxic necrosis with subsequent regenerative hyperplasia of marked degree (case 2) is included in the paper. The microscopic sections of liver in this case when contrasted with those of the infant's tumor in case 3 exemplify well the difficulties of diagnosis in distinguishing some cases of nodular hyperplasia (adenomatous regeneration) from well-differentiated primary carcinoma which is diffusely scattered throughout the liver. The lapse of time has disproved the biopsy diagnosis of primary carcinoma of the liver in case 2. Multiple sections from various portions of the tumor in case 3 as well as the metastasis in the humerus made the diagnosis of malignancy evident. The difficulty in distinguishing between the border line cases has been recognized.

Referable to this point are numerous articles in the older literature (Aschoff,[35] Rolleston,[36] Ribbert [37]).

Many of our cases were characterized by multiple nodules, often similar in size. Their distribution, however, was never uniformly diffuse and for reasons already stated we concluded that the evidence available favored an unicentric origin of them. The low "metastatic index" of primary liver carcinoma for extrahepatic organs is in striking contrast to the multiple spread of carcinoma throughout the liver.

Even though the tumors varied considerably in morphology, individual tumors were quite uniform in structure except for a few cases. In these cases there existed not only considerable pleomorphism in the primary tumor, but also quite widely divergent cellular arrangements in the metastases as contrasted to the primary. Syncytial multinucleated giant cells were found in 21 cases (43 per cent). The cells varied greatly in numbers and usually required considerable search before they were discovered.

Summary

1. We have studied a series of 49 cases of primary carcinoma of the liver in the records of the Department of Pathology of the Stanford University School of Medicine. Adequate clinical data were available for study in 40 of these cases and pathologic data in all of them.

2. Forty-seven of these cases or 96 per cent of them were males whereas only two were females. The occurrence of nine cases in Chinese (19 per cent) is striking in view of the relatively low percentage of Chinese to the total population. The age distribution was striking in that nine of the patients were 40 years of age or less. In one of these the neoplasm was probably prenatal in origin as an abdominal mass was discovered three days after birth. The infant died of primary carcinoma of the liver at three months of age.

3. The two classic types of primary epithelial liver tumors were observed in the series; of these 45 cases (92 per cent) were liver cell carcinomata, and only four cases originated in the epithelium of intrahepatic bile ducts (8 per cent).

4. The most commonly observed clinical symptoms were in order of frequency an abdominal mass, abdominal pain, jaundice, ascites, weight loss and edema of the legs. It is to be noted that these symptoms are non-specific in the sense that no grouping of them is characteristic or diagnostic of the disease. We were unable satisfactorily to correlate the clinical and pathologic data to the extent of establishing clinical criteria for the diagnosis of any particular type of primary carcinoma of the liver.

5. It is noteworthy that in 12 of these cases gross bleeding into the peritoneal cavity occurred and was a significant factor in causing death.

6. In one of our cases, a male aged 19 years with a primary liver carcinoma, marked clinical hypothermia was so striking as to warrant a report

in detail although we cannot definitely state that the hypothermia was the result of the neoplastic disease.

7. Cirrhosis as a co-existent lesion was found in 27 cases (54 per cent). Three of these were cases of hemochromatosis. It is striking that even though the incidence of portal cirrhosis has doubled in the past seven and a half years, the percentage of cases of cirrhosis associated with primary carcinoma of the liver has decreased slightly.

8. In 36 cases (73 per cent) the liver was increased in size. Peritoneal fluid was noted in 44 cases (90 per cent) and in 28 (57 per cent) exceeded 1,000 c.c. in amount.

9. Many of the tumors were anaplastic. However, bile formation was demonstrated in 17 of them (35 per cent).

10. The incidence of extrahepatic metastases is low. Organs other than the liver were involved only 26 times (metastatic index 0.53) in contrast to 44 cases (90 per cent) in which intrahepatic metastases occurred.

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DISSECTING ANEURYSM OF THE AORTA IN YOUNG INDIVIDUALS, PARTICULARLY IN ASSOCIATION WITH PREGNANCY. WITH REPORT OF A CASE *

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UNTIL attention was called to it [1, 2] coronary occlusion below the age of 40 was considered rather unusual.

Similarly, in the past dissecting aneurysm of the aorta has been held to occur almost exclusively in older individuals particularly in the presence of hypertension. The authors' interest in the occurrence of dissecting aneurysms in young individuals was stimulated by the following case which occurred in a woman of 22, 12 days post partum. Because of this case it became of interest to find out just how common or uncommon dissecting aneurysm of the aorta is in young individuals, and a study has therefore been made of accessible reports of cases from the literature. This has shown a considerable frequency in patients under the age of 40. Further, it is interesting to find that, when the disease occurs in young females, it is frequently in association with pregnancy.

CASE REPORT

Mrs. B. J., aged 22, had been followed from 1936 to 1941. At the age of 17, while single, she was seen with "lumps on both legs," nervousness and constipation. The "lumps" were suggestive of erythema nodosum. The thyroid gland was slightly enlarged, and there were moderate varicose veins. No determination of the basal metabolic rate was made. In the latter part of 1938, while bathing, another girl struck her over the sternum during play. A soreness remained for a day or two. In November of 1938 she noticed a nodule in the upper outer quadrant of the right breast. She paid little attention to it, attributing it to the chest blow, but by June 1939 it had enlarged, pain appeared, and she entered the Lucas County Hospital. The complete history and physical examination were negative except in the record there were noted "mild dyspnea on exertion and pedal edema." This was never substantiated on subsequent observation. The heart was normal, rhythm regular at 72, blood pressure 130 mm. Hg systolic and 86 mm. diastolic. Laboratory studies showed essentially normal blood and urine. Because of a family history of diabetes and tuberculosis a roentgenogram of the chest was taken (figure 1) which showed only "increased peribronchial thickening" and gave us an excellent control study of the heart and aorta. Unfortunately an electrocardiogram was not taken. The mass in the breast was removed under nitrous-oxide-oxygen anesthesia. The blood pressure throughout the procedure remained at 120–130 mm. Hg systolic and 70–78 mm. diastolic. Histologic study showed the mass to be a "pericanalicular fibroadenoma with intralobular fibrosis of the surrounding breast tissue."

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† This paper was completed before the author entered active military service.

The patient remained healthy and well and was married in June 1940. She was not seen again until March 1941 when she complained of amenorrhea since November 11, 1940. She denied any dyspnea or edema but occasionally had headaches and nocturia. The general examination was entirely negative except for a four months' pregnancy and a soft systolic murmur (grade 1) over the precordium. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Two months later she showed slight edema of the ankles and 1 plus albumin in the urine. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. In June, July and August examinations were negative; there was no albuminuria. On August 6, blood pressure was 148 mm. Hg systolic and 80 mm. diastolic. Expected term was August 18, 1941.

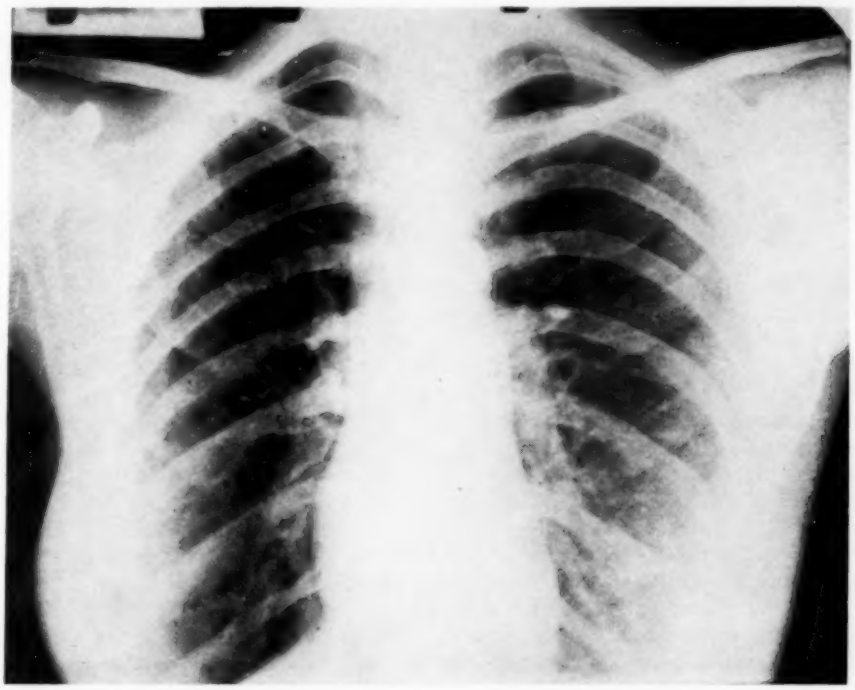

FIG. 1. Teleroentgenogram of the chest taken in June 1939, approximately two years before the fatal illness, showing a small heart and a normal aorta.

She entered the obstetrical service of Toledo Hospital on August 16. At this time the family history revealed death of the father at 34 with "heart trouble"; the mother was living, with diabetes; a sister had tuberculosis that had been treated by pneumothorax. She had had chicken-pox and diphtheria at six and seven, and pneumonia at 17. There was no history of measles, mumps, whooping cough, scarlet fever, rheumatic fever, tonsillitis, chorea or epistaxes. The tonsils had been removed at the age of eight. The cardiorespiratory history again revealed no pain, palpitation, dyspnea, cough, sputum, hemoptyses or night sweats.

The physical examination was essentially normal. The heart was recorded as "negative." Blood pressure was 115 mm. Hg systolic and 65 mm. diastolic. The infant was in cephalic presentation, R.O.T. Labor progressed normally under nembutal and scopolamine analgesia. When the cervix was fully dilated, labor was

terminated by episiotomy and elective forceps under ether anesthesia without difficulty. The child was a normal male, weight 8 pounds, 3 ounces.

For the next 10 days at bed rest the baby and mother did splendidly. The patient's temperature was normal, pulse 80–85, respirations 20. She then was allowed up gradually, and at about 10 o'clock on the morning of the twelfth day, while seated quietly on a radiator and visiting with another patient, she was seized suddenly with a terrific "tearing pain" and "crushing" sensation beneath the sternum. It was felt also in the epigastrium and in the mid-thoracic spine in the back with a "choking sensation" in the throat and radiation of pain with numbness into both shoulders and arms, and numbness in the legs, greater in the right. She became acutely short of breath, had moderate cyanosis and developed extreme weakness. She remained conscious. Since it was thought that this was probably a pulmonary embolus, she was given morphine sulfate 1/6 gr. and nembutal 1½ gr. Half an hour later, upon arrival of one of us at the hospital (C. A. B.), this medication had given no relief. In the interval she had vomited brown material. Upon examination at 10:30 the patient was acutely ill, pale, with moderate cyanosis, marked throbbing of the neck vessels, coarse murmurs over the heart and a blood pressure of 170 mm. Hg systolic and 0 mm. diastolic. Temperature was 99° F., pulse 100, respirations 28. She was given more morphine but relief was not complete.

She was seen in consultation (M. A. S.) at 5:00 p.m., seven hours after the onset of pain, at which time the following were noted:

The patient was conscious but very acutely ill. There was moderate dyspnea but no evident cyanosis at this time. She complained of "numbness" of both shoulders, "suffocation" in the throat, particularly on taking a deep breath, and pain down the entire length of the spine and down the right leg to the toes. There was now little discomfort in the left leg. There was no stiffness of the neck. The fundi were negative, as seen through pupils constricted by morphine, except for arterial pulsations. There was no significant distention of the neck veins. There was active throbbing of the carotid arteries and a large suprasternal pulsation over which a harsh thrill was felt and a to and fro bruit heard. The supracardiac dullness was widened to percussion. There was a coarse, vibrating systolic thrill over the base of the heart. Over the entire precordium there was a long, harsh systolic murmur (grade 5) and a coarse, long diastolic blow, loudest over the aortic area. Both heart sounds were present and loud. Over the pulmonic area the diastolic blow was softer and perhaps suggestive of pulmonic insufficiency (? transmitted from aortic area). These murmurs were transmitted widely over the chest and into the neck vessels. The rhythm was regular and rapid at 90. Blood pressure in the right arm was 180 mm. Hg systolic and 50 mm. diastolic, in the left arm 180 mm. systolic and 50 mm. diastolic. The lungs were clear. The liver extended two fingers'-breadth below the costal margin, was smooth and slightly tender. The spleen was not palpable. Pelvic and rectal examinations were not done. The spine was tender to light percussion from the first thoracic to the sacrum. The extremities were cool, slightly moist, with no evident cyanosis. The reflexes were normal; there was no edema. The pulse was full and bounding, of Corrigan type, in both arms and legs. Blood pressure in the right leg was 170 mm. Hg systolic and 40 mm. diastolic, in the left leg 190 mm. systolic and 60 mm. diastolic.

It was concluded that we were dealing with an acute severe vascular accident, most likely a dissecting aneurysm of the aorta, possibly rupture of an aortic valve cusp.

Laboratory examination showed hemoglobin 11.0 grams (70 per cent), erythrocytes 4,110,000, leukocytes 19,800, with 64 per cent segmented neutrophiles, 17 per cent nonsegmented forms, 11 per cent lymphocytes, and 8 per cent monocytes. A bedside roentgenogram of the chest and an electrocardiogram were made promptly.

The chest film is shown in figure 2, for comparison with figure 1 taken two years previously. In figure 3 are shown four electrocardiograms taken (1) August 28, 24 hours after the accident, (2) August 30, (3) September 2, and (4) September 5, 1941. The blood Wassermann and Kline reactions were negative. Within 24 hours the temperature rose to 102° F. where it remained for eight days, rising to 106° F. before death. The pulse rose and remained at 120, full and bounding; the respirations remained at 30.

The next day a harsh to and fro pericardial friction rub, superficial and easily distinguished from the murmurs, was audible over the base of the heart. Two days later it had disappeared. At the end of the third day there were a few râles at both lung bases but no sacral or pedal edema. A presystolic murmur, considered to be an Austin-Flint murmur, could be heard at the apex. Blood pressure was 180 mm. Hg systolic and 30 mm. diastolic. Rapid digitalization was begun. A distinct gallop rhythm also became audible. Blood cultures drawn on the first day still were negative after five days.

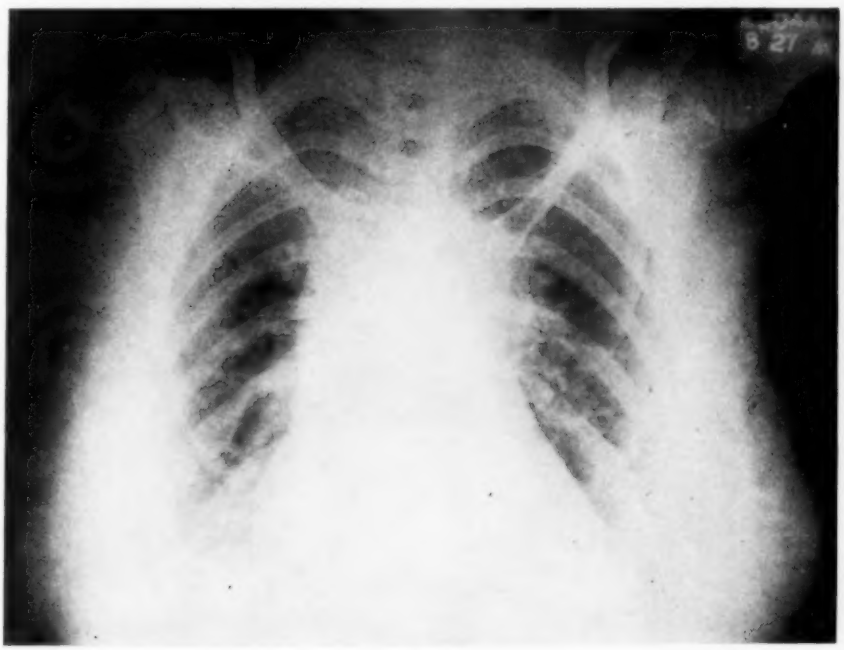

FIG. 2. Roentgenogram of the chest taken 24 hours after rupture of the aorta. In comparison with figure 1, note the enlarged heart, markedly widened aorta and beginning pulmonary congestion. (Bedside film.)

By the sixth day there was a return of cyanosis, marked pulmonary congestion, and rapidly increasing pedal and sacral edema. The patient had been completely digitalized and was on a maintenance dose of 3 grains daily. She began to vomit frequently so a Miller-Abbott tube was inserted and the patient was given subcutaneous clyses of glucose in saline.

Repeated catheterized specimens of urine showed no red blood cells. By the eighth day a moderate anemia had developed, with hemoglobin 66 per cent (Sahli), erythrocytes 3,450,000, leukocytes 28,400 with 78 per cent segmented neutrophiles,

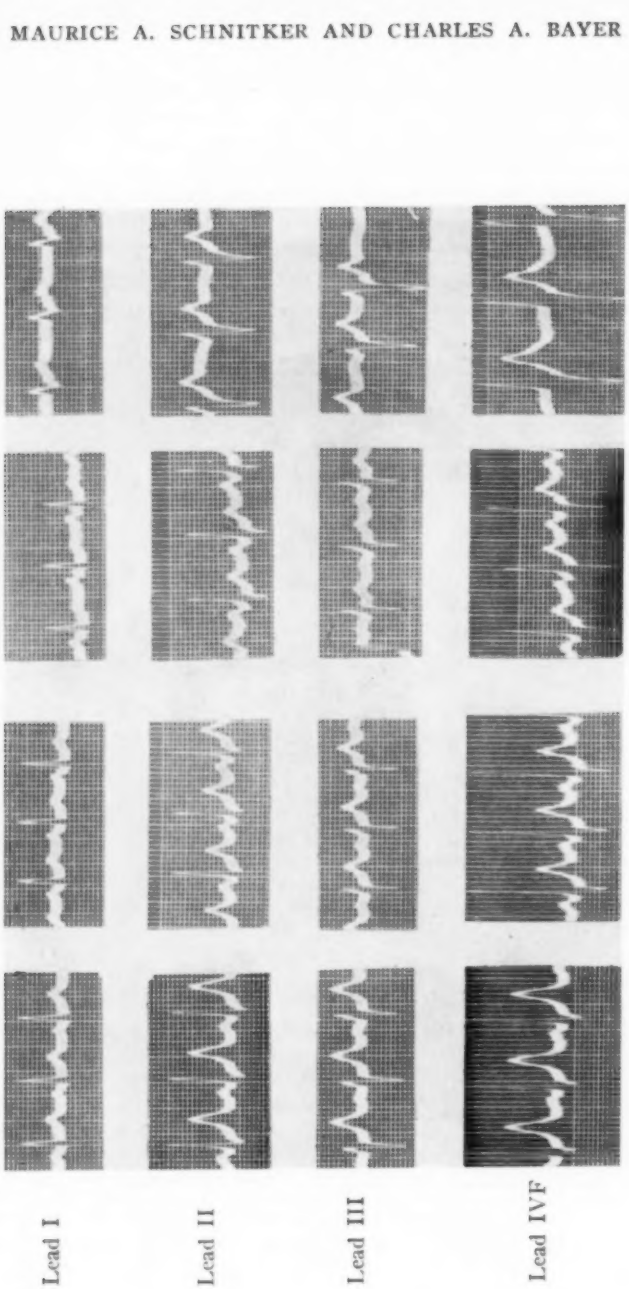

FIG. 3. Serial electrocardiograms taken during course of the illness.

12 per cent nonsegmented forms, 6 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophiles. The elevated white blood cell count also favored the diagnosis of a severe vascular accident.

The patient died 10 days after onset in severe cardiac failure with massive edema, rapid and weak pulse, cyanosis, cold extremities and marked dyspnea. Death was not abrupt as with terminal rupture of a dissecting aneurysm.

Autopsy by Dr. Bernhard Steinberg eight hours after death showed the following pertinent findings: (1) 100 c.c. of blood-tinged fluid were in the pericardial sac. (2)

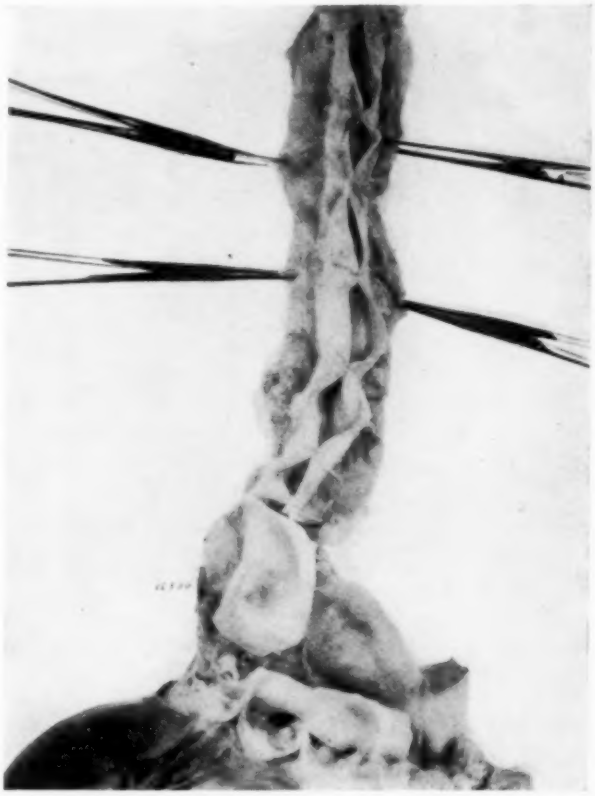

FIG. 4. Showing the very sharp, knife-like tear just above the aortic cusps. The intima is curled up upon itself; the forceps are grasping the adventitia.

The heart extended to the sixth interspace slightly past the mid-clavicular line on the left, weighed 350 grams, and there was slight dilatation of the left ventricular chamber but no other gross abnormalities. All the valves were normal. (3) The right lobe of the liver was enlarged and extended 8 cm. below the costal margin. (4) The aorta showed a complete transverse sharp tear in the intima, as if it had been cut with a knife, 3.5 cm. above the aortic leaflets. The torn intima was contracted. A dissecting aneurysm extended from the transverse tear to the renal arteries but did not include them (figure 4). There was no dissection in the walls of the major vessels to the arms or neck. The intima did not show any abnormal changes; there was no gross evidence of an atheromatous process. The lungs, liver, spleen and

kidneys showed only passive congestion. The uterus was almost completely involuted.

Microscopic Study: As shown in figure 5, the separation of the coats occurred in the outer third of the media. The tear was longitudinal in type with probably smaller longitudinal tears. Various sections showed what appeared to be a diminution in the amount of elastic tissue in the media. No areas of acellular necrosis were observed. There were, however, frequent small areas in which there was an accumulation of mucin-like material; its significance is not clear. The adventitia was edematous and contained a moderate number of cells which consisted of a proliferating fixed-tissue

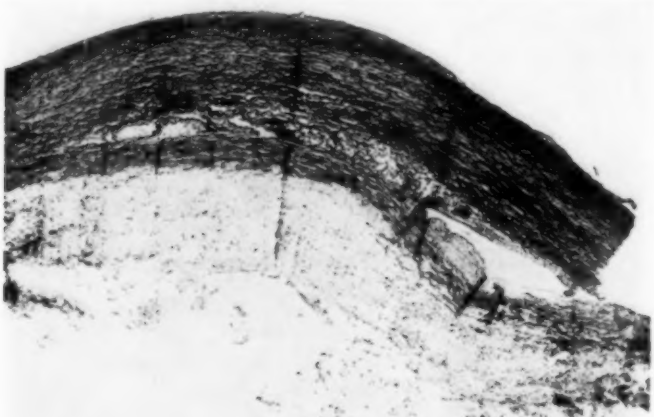

FIG. 5. Demonstrating an initial longitudinal tear occurring in the outer third of the media. (Verhoff's elastic tissue stain. Microtessar, mag. 45 diameters.)

type (endothelioid cells), larger mononuclears, and a sprinkling of polymorphonuclear leukocytes with an occasional lymphocyte. The cellular exudate tended to localize itself around blood vessels. The coat showing the least microscopic abnormality was the intima. There was an occasional small area of atherosclerosis.

Special preparations of sections with iodine and sulfuric acid for cholesterol study were not satisfactory.

DISCUSSION

There are many descriptions [3, 4, 5, 6, 7, 8] of dissecting aneurysms in older patients, usually males, between the ages of 40 and 65, with previous good health but with hypertension. Frequently in these cases, following some strenuous exertion or emotional strain, a sudden "tearing" or "ripping" pain had appeared beneath the sternum, in the back and perhaps in the abdomen. The pains may or may not radiate into the arms or legs. Frequently there is collapse, and the patient may die immediately. If he recovers from the collapse the pain may wax and wane, but the blood pressure remains elevated. Dyspnea and cyanosis may be present. After an interval varying from a number of hours or days to, occasionally, weeks, frequently as the patient

seems to be recovering, there is sudden death from rupture into the pericardium or a pleural cavity, commonly the left. In the interval, signs of all sorts may have developed as the result of tear or occlusion of vessels to the brain, kidneys, heart, extremities, etc. Ten per cent may recover,[5] that is, survive the acute attack.

Source of Material: Our study of young cases began with the finding of 45 instances under 40 years of age in Shennan's classical monograph.[6] In 1932 Klotz and Simpson [9] made special mention of 42 cases of the disease in individuals under 40, but their discussion is almost entirely about the pathologic lesions and not the clinical aspects. They do not give the source of their material. In their report of five cases, however, three were under the age of 40 which we chose to use.

The Younger Age Group: In addition to the above 48 cases, since 1933 we have been able to find data on 92 other cases under the age of 40, among which are included a few earlier cases not listed by either of the above authors. With the addition of our own case, there is a total of 141 instances of dissecting aneurysm of the aorta in individuals under 40 years of age. This is necessarily not a complete list because some of the European literature of the past two years is not available. But the point to be emphasized is the fact that in the available sources of information we have found a total of approximately 580 cases of dissecting aneurysms of all age groups on record, of which 141 or 24.31 per cent, approximately one in four, were under 40 years of age. The significance of this becomes even more apparent if we return briefly to a comparison with coronary artery disease. In the study mentioned previously Glendy, Levine and White [2] found an incidence of 1.54 per cent of 3,376 individuals with significant coronary artery disease to be below the age of 40, whereas in our analysis we find an incidence of nearly 25 per cent in dissecting aneurysm. Certainly this has not been appreciated.

Sex, Age and Race: Of the 141 cases comprising this study there were 92 males and 49 females. Some of the youngest instances on record are Bronson and Sutherland's case [10] in a boy of four and one-half years, Rokitansky's case [11] in a boy of eight years, Oppenheimer's case [12] in a girl of nine years and Wasastjerna's case [13] in a boy of 13 years. In the total series there are four cases between the ages of 1 and 10, 27 cases from 11 to 20, 53 cases from 21 to 30 and 57 cases from 31 to 40. Eleven, or 7.8 per cent of the total group, were negroes.

Hypertension: Hypertension of varying degree has been given considerable emphasis as an important underlying factor, and by many as a causative factor, in dissecting aneurysm of the aorta. Unfortunately, from the standpoint of clinical study, the nature of the disease in many cases is such that the individual dies almost instantly or within a very short time, so that certain pertinent observations cannot be recorded. But occasionally here and there throughout the literature there is expressed the thought that hyper-

tension is not an invariable factor, and in some series it has been more often absent than present.[6, 14] Shennan noted that in 131 of 163 cases in which the condition of the heart was stated, the left ventricle was described as hypertrophied and from that he assumed that some degree of hypertension had been present. In the remaining 32 cases (20 per cent) there seemed to him to have been evidence that high blood pressure, at least a permanent rise, was not an invariable factor. In two of his cases (case nos. 44 and 114) the hearts were described as even atrophied. In Mote and Carr's recent series of 64 cases the blood pressure had been recorded in 26; it was found to be elevated in seven and *normal in 19*. Our own case had frequent determinations of the blood pressure over a period of four years and it was found always to be within normal limits. However, in connection with our case Dr. Soma Weiss[15] gave us an interesting thought in a discussion of this point: "I am suspicious, however, that this patient had high blood pressure before the accident occurred, for in my experience in dissecting aneurysm *after* the dissection occurs the blood pressure is *not higher* than before, and very often it is lower or remains the same. The fact that your patient had a blood pressure as high as 180 following the attack could suggest that hypertension had existed before. Why the blood pressure readings were normal we cannot explain, but those things happen." On the other hand, we have felt that the elevated systolic pressure after the accident occurred was accounted for on the basis of the altered dynamics occurring with the free aortic regurgitation (B.P. 180 mm. Hg systolic and 40–0 mm. diastolic), as is seen with syphilitic aortic insufficiency. On this basis it need not be assumed that previous hypertension had been present.

Although many times no blood pressure readings were given in the case reports in the literature, in this series of 141 cases under age of 40 we found a record of the blood pressure in 44. In 23 it was elevated, greater than systolic 150 or diastolic 95, and *in 21 it was normal*, below these figures. In 24 other cases in which the blood pressure was not recorded the heart was described as "enlarged" or "hypertrophied," particularly the left ventricle. Perhaps this may mean previous hypertension. But in the series of 44 cases with blood pressures recorded, which is hardly large enough to be of statistical significance, one gains the impression that in individuals under the age of 40 who suffer with a dissecting aneurysm of the aorta, about half have hypertension and half do not.

Now, in individuals under the age of 40 hypertension is much less frequent than it is over 40. So, if hypertension were such an important etiologic factor in dissecting aneurysm, we would have expected that at least as many, if not more of the younger group would have hypertension as is reported for older individuals with this disease. Yet in only half of the recorded cases was it present. We do not wish to imply that hypertension is of no significance in dissecting aneurysms, but we do not believe it to be as important as considered heretofore. Here again, a comparison with coronary artery

disease in individuals under 40 years of age is interesting, for in such cases Glendy, Levine and White [2] found hypertension is only 16.6 per cent of 96 cases. Therefore, although hypertension may be present, it would appear that in both conditions, coronary artery disease and dissecting aneurysm of the aorta, the chief factor in the etiology of an accident, i.e., occlusion in the case of a coronary artery, or dissection in the case of the aorta, is the underlying vascular disease and not the hypertension.

Since it has never been quite settled, particularly in the older age group, whether the so frequently associated hypertension can cause dissecting aneurysm without a preceding medial necrosis, one is forced to raise the question whether there are several, possibly three types, of dissecting aneurysm: (1) with medial necrosis alone; (2) with a stress break of the wall, possibly in elastic tissue, from trauma, or from hypertension, continued or temporary; (3) with a developmental defect in the wall. For the reasons given in the preceding discussion we feel satisfied that the presence of medial degeneration alone can give rise to a dissecting aneurysm. Hypertension need not be present. Our case showed a certain amount of medial degeneration, and hypertension was never present before the fatal illness. There are numerous similar instances without previous hypertension on record. The factors of trauma and developmental defects will bear further discussion.

Trauma: Approximately three years before the fatal illness our patient had received a "blow" to the sternum. She and her relatives minimized the severity of it. We seriously doubt that it had any relationship to her fatal illness. All through the older literature, however, the factors of stress, strain, injury, exertion or emotion are often given a prominent part in the etiology of dissection. Although in some instances the relationship between strenuous physical effort and the dissection seems so definite that it cannot be ignored, we wish to raise the question whether it also has not been overemphasized.

In this series of young individuals with dissecting aneurysms, a direct relationship with trauma, stress or strain, was given 12 times, an indirect relationship three times. By "direct relationship" is meant at the time, or a few minutes or hours before the accident. This group includes two cases occurring during labor. The cases with "indirect relationship" are ones with a history of fall, blow, etc., several weeks or months previously. It is conceivable that a fall, or severe strain, physical or emotional, could give rise to rupture of a medial vessel or vessels, as discussed under the mechanism of dissection, but unless the media were already deficient or degenerated this is not likely to happen. For the medial vessels are small, under low pressure, and the adequate structure of the coats of a normal aorta are sufficiently protective to those vessels.

Developmental Anomalies: Another factor in the etiology and mechanism of dissecting aneurysm that has been considered of some importance [5, 6] is congenital malformation, particularly hypoplasia and coarctation of the aorta.

Others have considered this a causative factor in a "small minority of freak cases." [7] To strengthen the idea of its importance many have quoted Abbott's studies [16] showing that 33 of 200 cases with coarctation died of dissecting aneurysm of the ascending aorta. Twenty-seven of those were under the age of 40 and had not been listed by others so they are included in our series. We were interested in an analysis of this subject from the opposite point of view, namely, how many in our younger age group had either distinct narrowing or coarctation of the aorta? In 45, or 31.9 per cent, of the 141 cases such an anomaly was described. This is of interest when contrasted with the "older age groups" in which only five of Shennan's cases over age of 40 had "slight isthmus stenosis." The significance of this appears to be twofold. First, it would seem that if a dissecting aneurysm occurs in an individual in the younger age groups there is a strong probability that hypoplasia or coarctation of the aorta may be present. It would also appear that the younger the individual, the more likely it is to be present. In the four cases from age 1 to 10 it was present once, in three not mentioned. In the 27 cases between 11 and 20 years of age it was present in 19, not mentioned in eight. After the age of 20 it became definitely less, for in the 53 cases from 21 to 30 it was mentioned as present in 17, and in the 57 cases between 31 and 40 it was recorded only eight times. Secondly, numerous pathologists have pointed out a "deficiency" in the coats of the aorta, particularly the media, when coarctation is present. This may give a condition favorable for dissection to occur. In several instances of coarctation with dissecting aneurysm, in which the descriptions of the pathologic lesions were adequate, the degenerative lesions in the media seemed similar to the Erdheim's necrosis found in practically all cases of dissecting aneurysm [9] in which adequate studies were carried out.

The higher incidence of such a congenital anomaly in the younger age groups may be in part an explanation of the etiology of dissection since hypertension was found less frequently in the group as a whole than in the older age groups. On the other hand, coarctation is characterized by hypertension in the upper extremities. In only two of the cases with coarctation in this series was hypertension noted; in 39 it was not recorded. However, many of the cases collected by Abbott and others, which we have found, occurred before the introduction of clinical sphygmomanometry. In four instances with only hypoplasia the blood pressure was normal. In 15 of the 45 cases, or 33 per cent, bicuspid aortic valves were present and the coarctation was "extreme." In our own case there was slight hypoplasia but no significant narrowing, and the aortic valves were normal. In the 33 cases of Abbott, 22 had the ductus arteriosus closed or ligamentous; in three it was patent; and in eight the condition of the ductus was not described. Shattenberg and Ziskind [17] mention other congenital factors which they believe may be of importance in the background of dissecting aneurysm of the aorta, namely, thymico-lymphatic constitution, cardiac hypoplasia, and aortic

stenosis. Slight aortic stenosis was present once,[17] and the other features we have not found described in this younger age group. There was one instance of subaortic stenosis,[18] and two others had a patent foramen ovale.[19, 20]

The Aortic Disease: It seems now to be generally agreed, since the excellent studies of Shennan,[6] Klotz and Simpson,[9] Moritz,[21] Leary and Weiss,[22] recently summarized by Sailer,[23] that the primary fault underlying dissection is a cystic type of degeneration (so-called Erdheim's medionecrosis cystica) of the media, the cause of which is still undetermined. It is our belief that this cystic degeneration is similar in all cases. Hypertension and trauma may act as initiating factors in the accident, but dissection can and does take place without them. A congenital anomaly, such as hypoplasia or coarctation may have associated medial degeneration which makes such cases subject to rupture. Infection may play a rôle, but syphilis seems to be unusual. It was present only five times in this series of 141 cases.

The Mechanism of Dissection: There are numerous texts and recent articles which continue to adhere to the idea that rupture takes place probably through the intima at the margin of, or adjacent to, an atheromatous ulcer. Thus it has been thought that the dynamic pressure of the aortic column of blood, by some expansile force or lateral wall pressure, causes a break in the intima with transverse, longitudinal, or skew tears resulting,[8] the aortic blood column then advancing into the media and progressing in that coat. This is rather difficult for us to conceive, particularly when the intima appears to be perfectly normal, grossly and histologically, as it was in our case.

We are inclined to agree with Mote and Carr and others [24, 25, 26, 27] that the accident begins probably in the media. In support of this idea are several observations. First, many times an atheromatous ulcer either has not been described or has not been found at or near the point of intimal tear. It may be argued, however, that the gross distortion which occurs in that part of the aorta involved in the tear precludes the finding of any previous ulcer or intimal abnormality. In our own case, with its clean, knife-like edge, there was no evidence, grossly or microscopically, of intimal abnormality. Secondly, practically all cases of dissecting aneurysm have shown varying degrees of medial necrosis (the aortic medionecrosis cystica of Erdheim) in addition to distortion caused by the actual dissection, indicating that this necrosis is a dominant preëxisting lesion. Thirdly, there are at least six instances on record [14, 24, 28, 29] in which a hematoma was found in the media at autopsy, with some dissection and *without any tear in the intima.* The intima remained intact. In some of these cases the medial disruption seems to have occurred in the outer third of the medial coat. Perhaps also significant is the fact that any nutrient vessels in the media are to be found in its outer third.

From these considerations we have been led to visualize the mechanism of dissection somewhat as follows. In an aorta in which there is a cystic type

of degeneration and some softening, there is a rupture of one or several medial nutrient vessels causing a hematoma of varying size in the media. The process may stop there, as mentioned above, with perhaps only one or two inches of dissection occurring. It is our opinion, however, that the majority of cases of dissecting aneurysm begin in that way. When such a hematoma grows large enough or rapidly enough, the stretching and weakening of the over-lying intima, possibly by a pressure necrosis, causes the intima to tear from without inward into the aortic lumen, transversely, longitudinally, or skew. This gives an opening that will allow the large column of aortic lumen blood, under its high pressure, to enter the aneurysm from the aorta and further dissect in the abnormal medial wall. It seems more reasonable to us to suppose that the entrance of blood from the aortic lumen into the media, under pressure, after the intimal tear, could carry the dissection onward than to presume that enough pressure exists in the medial nutrient vessels to "explode" with such apparent force as to cause dissection several feet in length and collections of large volumes of blood between intima and adventitia. After the dissection has occurred the containing wall of the aorta, which is then chiefly adventitia, is now under most unusual stress and strain. Hence, it is not difficult to see why it should give way later at some point with resulting external rupture into the pericardium, mediastinum, pleura or elsewhere.

On a much smaller scale, and under perhaps slightly different circumstances, much the same type of mechanism has been found to occur in coronary arteries with occlusion.[30]

The Site of Tear: Our case, like the majority, about 70 per cent,[31] occurred in the ascending aorta. The reason for this was studied by Rottino [32] who demonstrated that idiopathic, cystic medial necrosis, whatever its cause and whenever present, is to be found predominantly in the ascending aorta. The fact that arteriosclerosis is often minimal or less advanced in this portion of the aorta seems to be evidence against atherosclerosis as a basis of the mechanism.[48] In this series of 141 cases it was stated that the ascending aorta was the seat of the accident 58 times, and the arch or descending aorta six times. In 77 cases the site of the tear was not stated.

Aortic Insufficiency: Among the clinical findings should be mentioned the rather frequent occurrence of a murmur of insufficiency of the aortic valves. As in our case it may have diagnostic value, for we had the experience, as have several others,[28, 31] of observing the development of the murmur after the accident had occurred. Various explanations have been given for the mechanism of this murmur. One of the first, by Resnik and Keefer,[3] compared it to the dynamics that obtain in an arteriovenous fistula, explaining the peripheral signs of aortic insufficiency by an escape of blood from the original aortic channel into accessory channels formed by the dissecting aneurysm. The diastolic murmur and its propagation they attributed to the leak of blood through the breaks in the intima just above the aortic valves. A little

later Hamman [4] attributed the aortic insufficiency to an imperfect closure of the aortic valves due to distortion of the aortic ring by the nearby dissection. Subsequent studies on this point [14, 33] have failed to demonstrate significant structural alterations of the valves; and in many cases reviewed, in which a diastolic murmur had been present, it was found that either the tear of the intima was within 2 to 3 cm. of the valves, or the dissection had progressed cuspward to within the same distance of the valves. In our case the dissection had extended cuspward and the blood pressure became 180 mm. Hg systolic and 40–0 mm. diastolic. A loud murmur indicating free aortic regurgitation was present until just before death. The aortic cusps were normal but the ring was somewhat dilated.

Since a dissecting aneurysm is virtually a blood sac, or, if secondary rupture occurs back into the lumen, a sac within a sac, the volume of blood is still contained in the intact aorta (as far as the outer limiting wall is concerned) and is not escaping out of the vessel, as in the case of an A–V fistula, as considered by Resnik and Keefer. In our explanation we agree with recent authors that the insufficiency probably is due to weakening of the supporting elements of the aortic ring and proximal aorta, either by a tear or the presence of blood in the media in that location, with resulting "functional" dilatation of the aortic ring. A diastolic murmur interpreted as indicating aortic insufficiency was present in 34, 24.1 per cent, of the 141 cases. It was stated not to be present in 16 others, and in the remainder it was not mentioned. In Shennan's series it was not mentioned significantly. Holland and Bayley [8] suggest that the presence of aortic insufficiency may indicate that secondary rupture of the aneurysm into the pericardial sac is impending. In this series, of the 34 cases with aortic insufficiency, 21 terminated with rupture into the pericardial sac; in five others death was caused by congestive cardiac failure, and in two others by rupture into a pleural cavity. In our case death was due to cardiac failure with no secondary rupture into the pericardium. It may be true that the presence of aortic insufficiency forecasts possible rupture into the pericardium, for that clinical sign is present when the major involvement is in the root of the aorta. On the other hand, it should be remembered that in the vast majority of cases of dissecting aneurysm the terminal event is rupture into the pericardial sac.

Pericardial Friction Rub: On the second, third and fourth days a distinct and typical "leathery" to and fro pericardial friction rub was audible over the base of the heart in our case. It was very superficial in character and could be differentiated quite clearly from the systolic and diastolic murmurs present. At autopsy the pericardial lining was slightly roughened and the sac contained 100 c.c. of blood-tinged fluid. This finding was of interest in our case because of McGeachy and Paullin's statement [7] that a pericardial friction rub has not been observed in dissecting aneurysm. Further, the differential diagnosis of coronary thrombosis must always be considered when entertaining the possibility of dissecting aneurysm, and Levine [34] has used the

absence of a friction rub and cardiac irregularities in favor of the diagnosis of dissecting aneurysm. We have not found a pericardial friction rub described in any other case in this series.

Pregnancy: The most interesting feature that has presented itself in this study is the association of dissecting aneurysm of the aorta with pregnancy. Although we found one or two articles on this association in the German literature,[35, 36] it has received scant discussion in the English and American publications. Since the accident occurred so close to the gestation period in our patient, we were interested in securing more data on such a possible relationship. Our first striking finding was the fact that out of a total of 49 females in our series, in 24, or 49 per cent, the accident occurred in association with pregnancy. If one thinks of dissecting aneurysm as occurring only between the ages of 40 and 65 the question of pregnancy would rarely present itself. However, it seems to us very significant, statistically at least, that in half the women in this younger age group the catastrophe should occur during or immediately following pregnancy. The first obvious thought is, of course, a relationship to the strain and blood pressure changes that are known to occur with labor.[15, 35] When one analyzes the series, however, this cannot be the answer, for the majority occurred during the last trimester before labor had begun. In one case the pregnancy was "early," in one at three months, three at four months, one at six months, four at seven months, five at eight months, and five at "term." In only two cases was the dissection said to have occurred "with labor pains."[37, 38] In two cases, our own 12 days after delivery, and case 4 of von Recklinghausen[39] three weeks after delivery, the accident occurred post-partum. Most cases were primiparae. That the largest number should occur at the eighth to ninth month is of interest in view of the altered circulatory dynamics at this stage in pregnancy that have been demonstrated to occur by Burwell[40] and by Thompson[41] and their associates. In the last two to four weeks of pregnancy the pulse rate and circulation time remain slightly elevated, but there is a fall in cardiac output toward the normal. There is an elevation of venous pressure in the legs. There tends to be an increase in pulse pressure, but there is no significant rise in blood pressure. In fact, the diastolic pressure is apt to be lower than previously.

The fact that only half of the cases in this entire series in which the blood pressure was recorded had hypertension, that only two of eight cases with pregnancy in which blood pressure was recorded had hypertension, and the fact that 20 of the 24 cases occurred before labor had set in, with its elevation of blood pressure, seem to us again to demonstrate that hypertension is not of such paramount importance in the causation of dissecting aneurysm, at least in this younger age group.

What seems to us of more importance is an abnormal media, and possibly some other factors which are noted in the literature. Abbott[26] long ago pointed out the abnormal media that occurs with coarctation of the aorta.

This, and the incidence of such abnormalities in our series, has already been discussed. In only one case [42] of our 24 pregnant women was there "extreme stenosis" of the aorta, and in two others, McGeachy and Paullin's [7] and our own, was there slight hypoplasia. In the other 21 cases no mention of such abnormalities was made. In these three instances a congenital abnormality of the media may have been a factor in the etiology.

The other factors to which we refer concern changes that possibly may be brought about in the wall of the aorta by cholesterol. Schnitker, van Raalte and Cutler have found that the blood cholesterol becomes elevated following total thyroidectomy in man,[43] so the report of Kountz and Hempelmann [44] of three cases of dissecting aneurysm of the aorta following total thyroidectomy and the development of hypothyroidism is of great interest. It has been possible to demonstrate muscular and aortic degeneration in animals following removal of the thyroid gland, and Barr [45] has observed degeneration of the aortic muscle, as well as the smooth muscle of the intestinal tract, in a case of myxedema. Schultz [46] also has mentioned finding at necropsy mucinous infiltration of the media and adventitia of the aorta and carotid artery in a case of myxedema. Accepting the effect of cholesterol on the aorta as shown by the students of arteriosclerosis, we might reasonably suppose that the altered lipid metabolism which is known to occur during pregnancy may play some rôle in the occurrence of dissecting aneurysm during gestation. A second observation of interest is that of Leary and Weiss.[22] They report an instance of a rabbit fed cholesterol for approximately 156 days in which a dissecting aneurysm, very similar to that seen in man, occurred spontaneously. In further experiments with animals these authors were unable to induce a dissecting aneurysm by high cholesterol feeding alone, although medial changes occurred, but they could produce it by subsequent injections of adrenalin causing hypertension. The medial changes occurring in animals during high cholesterol feeding are very similar to those seen in human beings with a dissecting aneurysm. Finally, if disturbances in lipid metabolism in pregnancy were a causative factor in alterations in the media that might lead to a dissecting aneurysm, it would be of great interest to establish such aortic changes in pregnant women who did not develop a dissection, but died in or near pregnancy from some other causes. We have been unable to find any published studies on this subject, although Dr. J. L. Carr of San Francisco [47] has kindly told us that his observations have demonstrated a cystic medial necrosis of the aorta in pregnancy without dissection. What the cause of such medial changes during pregnancy may be is not known. Neither is their significance clear. But since we have found the incidence of pregnancy so high in dissecting aneurysms in the younger age groups the fact that they occur with pregnancy seems to us a most significant observation, worthy of further study.

In several cases on record the physician, alert to the serious situation that confronted his pregnant patient, hurriedly performed a Caesarean section in

an attempt to save the child. We have found six such instances, in three of which a viable infant was delivered. Another case, reported by Mote and Carr [14] is of interest also from an obstetrical point of view in that a viable infant was obtained by Caesarean section and the mother lived for another three years.

Termination. An analysis of our material shows that the duration of life after the attack is perhaps a little longer in the younger age group, possibly because of their otherwise better physical condition. In the older age group death occurs "from several hours to several days later." [6] In our younger age group the duration of life after the initial tear was given in 67 instances. "Sudden" and "instantaneous" death occurred in 10. Life continued less than an hour in four cases, from two to 12 hours in five cases, 12 to 24 hours in 12 cases. Death occurred within two days in six cases, one week in nine cases, and in two weeks in eight cases. Life continued for as long as a month in four cases, in one case two months, in one case five months and in another case eight months. There were four cases that lived for "some years," two, three, and 15 years. The longest case in our younger age group was an athlete, reported by Hall,[19] in whom the accident occurred at 17 and who died with cardiac failure at age 32.

The terminal event seems to be much the same in both age groups, however. In 152 of Shennan's 171 cases of recent dissection in which the intrapericardial aorta was involved, rupture took place into the pericardium (nearly 90 per cent). In this younger series the termination was given in 113 cases. Of these 88 (or nearly 78 per cent) ruptured into the pericardial sac. Of the remaining cases, three ruptured into "pericardium and pleura," eight into a pleural cavity, usually the left, and seven died with congestive cardiac failure. The cause of progressive cardiac decompensation in such instances remains obscure for no definite myocardial degeneration or inflammation has been noted in these cases at necropsy. Nevertheless it is an interesting phenomenon, for it demonstrates that a heart that has been, to all intents and purposes, perfectly normal, as in our case, can fail when such a terrific burden is placed upon it for an extended period of time. As a matter of further interest, in 66 cases which Shennan classified as "chronic," over the age of 40, the cause of death was "heart failure" in 30, nearly half. The incidence of other phenomena, such as blindness, paralysis, cerebral hemorrhage, visceral infarction, etc., we have not attempted to study statistically in this younger age group because of tremendous variations depending upon the degree and extent of the rupture.

Other Observations of Interest—The Electrocardiogram. In the relatively few cases in which electrocardiograms have been taken after a dissecting aneurysm of the aorta had developed, no consistent changes of marked degree have been observed. The most notable have been variations in left axis deviation and some T wave changes, such as flattening and occasionally slight inversion. In a few instances the alterations have been suggestive,

or even definite, for acute myocardial infarction following coronary occlusion. Such changes, for the most part, have occurred when the aortic dissection, or the blood, extended proximally to involve one or the other openings of the coronary arteries. In our case the striking features were changes indicating severe strain on the heart muscle, particularly the left ventricle. Unfortunately no tracings had been taken during her previous hospital admission. The first tracing, taken nearly 24 hours after the accident, shows a depressed ST_2 and very prominent S_3, and tall T waves in Leads II, III and IV. In the subsequent five days there was relatively little other change except progressive lowering of the T waves in all the leads. Finally, in the last tracing taken three days before death when cardiac failure was becoming severe, there is shown spreading and thickening of complexes indicative of exhaustion of the heart muscle. Except for the evidence of severe muscular strain and occasionally of coronary insufficiency if a coronary artery is involved in the process, the electrocardiogram does not appear to show features distinctive of dissecting aneurysm of the aorta.

Another feature of diagnostic value to us in our case was the *progressive anemia*. Originally in our differential diagnosis we considered coronary thrombosis, rupture of an aortic cusp, rupture of the aorta into the pulmonary artery, and ruptured chorda tendinea. In none of these conditions should there be a rapidly progressive anemia unless the ruptured aortic cusp or the ruptured chorda tendinea occurs in association with subacute bacterial endocarditis. Repeated blood cultures were negative in our case, and there was no previous valvular or congenital heart disease. She had had no fever. In the other conditions considered the blood is still within the circulatory vascular bed and an anemia would not be expected to develop. On the other hand, in dissecting aneurysm of the aorta a large amount of hemoglobin and red blood cells are taken out of the circulation, as in hemorrhage, and being contained in the aneurysm, probably in a clot, would give rise to a reduced count in the peripheral circulation. This occurred in our patient and was to us further evidence in favor of the diagnosis of dissecting aneurysm. Furthermore, it seems not unreasonable to suppose that the rapidity of development and degree of anemia may indicate also the severity and length of the tear.

Another guide which we used in attempting to estimate the extent of the tear was the presence or absence of *hematuria*. On repeated examinations of catheterized specimens of urine no red blood cells were ever found, which caused us to conclude that the rupture had stopped above the level of the renal arteries, even though she had experienced severe pains in the legs. Autopsy showed that the dissection had ended "just above the renal arteries."

A comment that has occurred occasionally in the early literature on dissecting aneurysms [50] concerns the frequency of concurrent *chronic nephritis*. In the older age group of dissecting aneurysms, if hypertension is present, a certain amount of chronic nephritis is to be expected with the hypertension

and vascular disease. Then, too, with renal infarction that may occur following involvement of one or both renal arteries by the dissection, one is led to wonder whether the resulting urinary findings, and perhaps even the kidney changes, were interpreted as being due to "chronic nephritis." In this series "nephritis" was recorded in the autopsy protocols in 11 of 141 instances. One of these was an "acute nephritis" in a boy of 15 with hypertension, one a "chronic nephritis" in a woman of 30 whose blood pressure was not given. The other nine instances occurred between the ages of 30 to 40. Of these, hypertension was known to be present in six and two of these died in uremia. In one other case "renal infarction" was described as such. The only finding of significance in our series seems to be that if "nephritis" is present it occurs most aptly in the older age group, in those who have hypertension. Nephritis was present in one of the pregnant cases.

Concerning other associated diseases it is of interest that dissecting aneurysm of the aorta seems to occur also in patients with *rheumatic heart disease*. In this series of 141 cases we found nine instances of rheumatic heart disease, eight with a mitral lesion and one with a slight aortic stenosis. This is an incidence of 6.38 per cent. One of the eight had a combined mitral and aortic involvement. Only one of these was pregnant, six months, a white female of 39.[9]

In view of the interesting observations made recently by Chapman, Dill and Graybiel [51] on the effect of severe spinal deformity on the heart and circulation, it may be of casual interest to mention that two of the cases in this series of dissecting aneurysm had "severe kyphoscoliosis." [52, 53] Whatever relationship there may be is not clear. One of these was in a case of pregnancy.[52]

Summary and Conclusions

A case of dissecting aneurysm of the aorta occurring in a female of 22 years, 12 days post partum, is presented. The accident occurred while at rest in an apparently healthy individual without previous hypertension or significant trauma. The diagnosis was made clinically. Death occurred with severe congestive cardiac failure 10 days later.

Because of the youth of the patient and the somewhat unusual circumstances of the case, we became interested in studying other cases of this disease in young individuals and the circumstances surrounding their illness. We used 40 years of age as a dividing line, and having found a significant number occurring in individuals under 40 years of age, we made certain comparisons between the features in this age group and the features manifest in older individuals with dissecting aneurysm. Only cases proved by autopsy were used. From such a study we have drawn the following conclusions:

1. Dissecting aneurysm of the aorta is far from rare under 40 years of age. Up to the present time there is on record a total of approximately 580 cases of this condition, of which 141, or 24.31 per cent, were under the age

of 40. It is evident that this high percentage has not been appreciated. This high incidence in younger individuals is of further interest when compared with other serious vascular accidents from which dissecting aneurysm must always be differentiated, such as coronary occlusion, in which Glendy, Levine and White found the incidence under 40 years of age to be approximately 1.54 per cent.

2. In all general discussions of dissecting aneurysm of the aorta in the literature, hypertension has been considered to be a most significant factor. Except as modified by the possible presence of coarctation of the aorta, hypertension occurred in only half of the cases in this younger age group in which data were available. It was not present as often in this group as in older individuals with this disease.

3. Trauma, in direct relationship, did not appear to be a significant factor in the younger age group.

4. The underlying lesion, regardless of the circumstances or associated phenomena, in both young and old individuals, appears to be a degenerative, cystic necrosis of the media.

5. In the younger age group there was found to be present a rather high incidence of congenital narrowing of the aorta, varying in degree up to extreme stenosis, and coarctation. This was found to occur in 31.9 per cent of the 141 cases. Such a finding has not been described in many of the cases over the age of 40. An aorta with coarctation has frequently a degenerated media, and this association of abnormalities is undoubtedly an important factor in the occurrence of a dissecting aneurysm in young individuals.

6. Another possible cause of medial degeneration leading to dissecting aneurysm, in this younger age group, may be the altered blood lipids that occur in pregnancy. For in this series of 141 cases there were 49 females, of whom 24, or approximately 50 per cent, were pregnant. This high incidence of pregnancy in dissecting aneurysm of the aorta in young individuals also has not received widespread appreciation. This study demonstrated further that the exertion and strain of labor apparently was not an important factor in the rupture, for in 20 of the 24 cases the accident occurred before labor had begun. In eight of these 24 cases the blood pressure had been recorded, and only two had hypertension. One pregnant case had coarctation of the aorta; two others had hypoplasia.

7. The duration of life seemed, on the average, to be slightly longer after the accident had occurred in this younger age group than in older cases. The only apparent reason for this seemed to be the better general condition of the younger patients.

8. The termination was similar in both age groups, i.e., 78 per cent in the younger, 90 per cent in the older, died with secondary rupture into the pericardium. A few others died with rupture into a pleural cavity, and death with congestive cardiac failure was somewhat unusual. If the disease

becomes chronic, about half of the patients die with progressive cardiac failure (Shennan).

9. Our case appears to be the first on record in which a distinct pericardial friction rub was observed over a period of nearly three days. A pericardial friction rub may favor a diagnosis of myocardial infarction but does not rule out a dissecting aneurysm. A progressive anemia may be regarded as favoring a diagnosis of dissecting aneurysm over coronary occlusion. The cause of the anemia is the decreased volume of circulating blood because a large amount is retained as a clot in the aneurysmal sac.

10. In the younger age group dissecting aneurysm of the aorta occurs occasionally in patients with rheumatic heart disease. Nine of our 141 cases, 6.38 per cent, had rheumatic heart disease.

11. An explanation is offered for the mechanism of dissection. It is believed that the accident begins as a hematoma in the outer third of a degenerated media. As the hematoma increases in size it causes rupture of the overlying intima. This opening allows the aortic column of blood, under its pressure, to carry the dissection onward between intima and adventitia, dissecting with the explosive forcefulness which characterizes this disease. That extravasated blood from medial nutrient vessels alone could exert enough pressure to cause sudden and widespread dissection would seem to be unlikely.

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THE RAW FOOD DIET: A THERAPEUTIC AGENT*

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Introduction

The Raw Food Diet may well be defined by a literal translation of the words of Bircher-Benner [1] who began using the so-called Rohkost Diät in 1895: "a diet composed exclusively or predominantly of edible plant life (fruits, leaves, roots, nuts, seeds) in uncooked condition, with exclusion of meats, eggs, cheese, white flour, extract sugar, alcohol, sodium chloride. . . ." He observed that this type of diet exercised a "far reaching, nonspecific therapeutic influence" on many kinds of human disorders, and in 1897 he opened his clinic in Zürich for the treatment of the sick with food. The rationale for this practice was not based on any known scientific principle but rather on such ideas as the notion that the heat of cooking possibly spoils the biological powers of vegetables and the questioning of the nutritional value of meat, inasmuch as beasts of prey eat blood, entrails, fat, and bone before touching the muscles. As time went on, certain of the pragmatic principles were more securely established through laboratory research. For instance, vitamins were discovered, and it was demonstrated that some of them were indeed destroyed by heat. The Bircher-Benner enterprise grew tremendously and has in large measure accounted for the current popular interest in raw foods.

I dare say that most physicians have had some sort of experience with raw plant products used as food. Some have heard of the subject only as an old wives' tale. Others have encountered patients who related that they had been crippled for years with arthritis or inflammatory rheumatism, had seen many doctors, had tried everything to get relief, and had finally hit upon the Raw Food Diet which had cured them. Some of you have heard the same story from erstwhile victims of headache, asthma, various kinds of "congestion," constipation, and so forth. Many undoubtedly know of the numerous vegetable and fruit juice-extractors, presses, and shredders which are on the market. I say this because of the rapidly increasing sales throughout the country of these units for home use. They are also employed by restaurants and food counters specializing exclusively in the Raw Food Diet, and by so-called "Vitamin Bars" where one buys "health cocktails," of which a popular one is prepared from the juices of celery, carrots, and parsley. Then there are those of you who know of the Raw Food Diet as a mainstay in the scheme of certain quack-cures conducted in unprincipled "clinics" where the tricks of the trade include colored lights and hocus-pocus baths. Finally, I might remind you of the relatively recent

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vogue of offering little raw tomatoes, raw sliced carrots, and chunks of raw cauliflower as appetizers at cocktail parties and buffet suppers.

I have emphasized the lay and commercial interest in the use of raw plant-products because in this country it is so much greater than the professional interest. A search in the Index Medicus reveals that the first reference listed under *"Food, Raw"* appeared in volume II for 1928. Between then and January 1941 there were altogether 89 articles on the subject of which only four were in the English language. As further indication of the lack of medical interest in the Raw Food Diet, one can find no pertinent discussions in recent textbooks of nutrition and of medicine. To probe deeper I have consulted the dietitians of prominent and representative hospitals in seven large cities in different parts of the United States, and in no instance have I learned of the use of the Raw Food Diet, either as one of the standard measures or in special investigative work. It is, therefore, primarily my purpose through this paper to stimulate interest in this subject not only among research workers but general practitioners as well.

In view of the war it is worth noting that of the 85 foreign articles mentioned above, 65 were written in German. It is probable that this source of information concerning the Raw Food Diet will be unproductive for some time to come. Hence, we must glean all we can from what writings are still available. In particular I should like to review the contributions of Hans Eppinger, Professor of Medicine at the University of Vienna. In the spring of 1938 I had the privilege of working as a voluntary physician in his clinic and thus had the opportunity to observe the practical application of the Rohkost Diät.

Scientific Basis. Eppinger [2] has described an experiment of fundamental importance performed on a marine unicellular alga, the valonia. This cell lends itself nicely to study because it is as large as a hen's egg and its contents can easily be tapped with a hypodermic needle. In its normal state, the valonia has been found to contain 4.0 per cent potassium and 0.23 per cent sodium. Inasmuch as the surrounding sea water is composed of 0.05 per cent potassium and 1.5 per cent sodium, the question arises as to the mechanism by which this cell can maintain its internal environment. Eppinger explains it on the basis of selective permeability exercised by the membrane of the healthy cell. If the valonia is poisoned with N/500 ammonia, it loses its ability to retain potassium and becomes a structure with merely a semipermeable membrane. The forces of osmosis and diffusion of electrolytes immediately introduce sodium into the cell as potassium leaves. Sodium, the powerful hygroscopic ion, carries water with it causing swelling and finally disintegration of the cell.

Carrying this principle over into the animal kingdom, Eppinger points out a proper analogy in that human cells also have their peculiar chemical composition despite the entirely different nature of the fluids in which they are bathed. Table 1 shows this contrast between blood serum and various

organs. If the electrostatic potential difference between the blood stream and the parenchymal cells is reduced through some pathological process like the so-called Seröse Entzündung,[3] there results a shift in electrolytes and water similar to that described in the valonia experiment. The potassium level in the blood rises and the total potassium and phosphate excretion is increased. Sodium chloride is retained and in a large measure accounts for the histological picture of edema and cloudy swelling in the involved organs.

TABLE I

Various Chemical Constituents of Certain Tissues Recorded as Milligrams Per Cent

	Na	K	Ca	Cl	PO_4
Serum	335	17	10	365	3
Muscle	96	290	4	33	186
Liver	133	337	6	93	4000
Brain	156	366	16	160	2600
Heart	133	278	7	111	139

In accordance with the above conception Eppinger felt that in certain diseases the Raw Food Diet would be of therapeutic value, because it is rich in potassium and poor in sodium. He argued [4] that the intake of such a diet would promote the excretion of the abnormal amounts of sodium chloride and water retained, for instance, in congestive heart failure, the nephrotic syndrome, subacute yellow atrophy, rheumatoid arthritis, and pneumonia. It is interesting in this connection to contrast his teaching with that of the eminent Americans, Russell L. Cecil [5] and James S. McLester,[6] who recommend giving pneumonia patients liberal quantities of milk and broths. Eppinger specifically forbids these items because of their sodium chloride content. Both schools recognize the well known fact that in pneumonia the chloride content of the blood and urine is diminished. On the one hand this is interpreted as indicating a loss of salt from the body as a whole, but on the other, as indicating a shift of salt into the tissues themselves. The solution to this question is of obvious importance, since the two corrective measures advocated above are diametrically opposed.

The Raw Food Diet as employed by Eppinger is more liberal than that defined in the first paragraph of this article. Skipping over the liquid and semisolid modifications for the particularly sick patients, the full diet may be described by the accompanying typical menu.

TABLE II

Breakfast: Raw fruit. Tea with lemon and sugar. Soft cooked egg. Salt-free bread and butter. Marmalade or honey.
Luncheon: 200 to 300 grams of raw vegetables. Mayonnaise. Raw fruit. Salt-free pastry (like a cherry tart).
Tea: Like breakfast, without the egg.
Supper: Cheese souffle or salt-free pancakes with fruit preserves or jelly omelette. Raw fruit. Nuts.

This diet is rich in carbohydrate, potassium, and some of the vitamins, but poor in protein, sodium, and calcium. It is emphatically not a proper diet for a healthy individual, and for the sick it should not be continued for more than five or six weeks. The success of the diet depends greatly on the skill with which the dishes are prepared.[7] Salads, compotes, vegetable and fruit juice cocktails offer abundant possibilities to the creative imagination of the culinary expert.

Clinical Application. Turning now to the clinical application of the Raw Food Diet I should like briefly to present four illustrative cases treated in Eppinger's clinic. The first is borrowed from a published report by the assistants, Beiglböck[8] and Faltitschek. It must be noted that the so-called molecular quotient of Na/Cl[9] refers to a quantitative relationship between the amounts of these ions excreted in the urine. A value of 1.0 is normal. Less than 1.0 indicates Na-retention within the body. This test and the quantitative test for albumin are done on 24 hour specimens.

Case Reports

Case 1. A 29 year old woman developed a sore throat with high fever, which subsided within a few days. Three weeks later her eyelids and hands grew swollen. Albuminuria and elevated blood pressure were found. She improved quickly on a meat-free, saltless diet. After several months she again developed a sort throat, and the above signs and symptoms returned. Thereupon she entered the clinic.

She was very pale. The eyelids and hands were edematous. The systolic blood pressure ranged between 125 and 135 mm. Hg. No abnormality was seen in the eye grounds. The urine contained about 1 per cent albumin, occasional fine granular casts, many red and white blood cells. The red blood cell count was 4,000,000; hemoglobin 70 per cent; white blood cell count 11,000 with 80 per cent polymorphonuclears. The blood serum non-protein nitrogen was 42 mg. per cent, and NaCl 586 mg. per cent. A sedimentation rate was fast at 35 mm. in one hour. On the concentration-dilution kidney function test a specific gravity of 1.024 was obtained, but the excretion volume was abnormally low.

For a few days of observation these values remained about the same except for the non-protein nitrogen which rose to 58 mg. per cent. The patient was then put on the Raw Food Diet, whereupon her condition improved, the hematuria disappeared, and the albuminuria diminished to 0.1 per cent. After a number of days the Na/Cl quotient became constant at 0.9–0.97, which was nearly normal. At that point the diet was changed to routine hospital fare, and within four days the facial edema returned, followed by widespread puffiness. The blood pressure rose 30 mm. Hg, the water balance was unfavorable, and the patient complained of headache and fatigue. The Na/Cl quotient fell to 0.30. The albuminuria rose to 0.6 per cent and the non-protein nitrogen to 160 mg. per cent. Thereupon the patient began to vomit, and the diet was changed back to Raw Food. Gradually over an eight day period the Na/Cl rose to 3.2, indicating a large excretion of Na. The 24 hour urinary output rose to 1500 c.c. The non-protein nitrogen returned to 57 mg. per cent, the albuminuria was reduced to a trace and the edema disappeared.

The diagnosis in the above case was subacute nephritis. Attention is called to the sodium retention which accompanied the change to regular house diet and the simultaneous aggravation of the disease: rises in non-protein

nitrogen, albuminuria, and blood pressure with reappearance of the edema. Resumption of the Raw Food Diet apparently effected a reversal of this disease process.

In presenting the three other cases, which were also under treatment in Eppinger's clinic, I shall describe my personal observations.

Case 2. A 59 year old woman was admitted on March 29, 1938, complaining of nausea. Except for a nervous breakdown two years before, she had been in good health until the preceding October when nausea came on especially in the morning. For three weeks it had been worse, and she noticed dryness of the mouth, loss of appetite, roughness of the skin, and dizziness. During this period she lost six pounds in weight. The physical examination was remarkable only in that her breath was uriniferous and the skin, very dry. The blood pressure was 190 mm. Hg systolic and 100 mm. diastolic; the temperature was subnormal. The urine contained 0.4 per cent albumin, coarsely and finely granular casts, and a few white blood cells. The red blood cell count was 4,100,000; the hemoglobin 60 per cent; the white blood cell count 10,600. The serum non-protein nitrogen was 117 mg. per cent. The volume of the first 24 hour urine specimen was only 500 c.c. with a specific gravity of 1.006.

For the first three weeks she was kept on a bland, salt-free diet. The Esbach reading of albumin in the urine fell to 0.2 per cent, the blood pressure remained about the same, the urinary output and specific gravity became normal, but the non-protein nitrogen rose to 170 mg. per cent.

Thereupon a change to the Raw Food Diet was made and maintained for the next three weeks. The Esbach reading fell further to 0.05 per cent. The blood pressure was reduced to 170 mm. Hg systolic and 70 mm. diastolic; the non-protein nitrogen, to 46 mg. per cent.

An ordinary bland diet was then instituted. Within one week the Esbach reading was 0.15 per cent; the blood pressure 210 mm. Hg systolic and 75 mm. diastolic; the non-protein nitrogen 71 mg. per cent.

The diagnosis in this case was chronic nephritis without edema. The Raw Food Diet apparently influenced the condition of the kidneys favorably as judged by the controlled effects on the albuminuria, blood pressure, and non-protein nitrogen. The biochemical-physiological mechanism at work in this instance is not clear.

Case 3. A 31 year old woman was admitted on May 9, 1938, complaining of palpitation. The past history was very complicated. She had had four sinus operations, appendectomy, a pelvic operation for an adnexal tumor, tonsillectomy, and an operation for ectopic pregnancy. Medically, she had taken a tuberculosis cure in Switzerland following an hemoptysis at the age of 11. At 20 she developed fever, arthritis, and endocarditis. Five years later she became very ill with thrombophlebitis in both legs and the right arm associated with massive edema. On the Raw Food Diet she lost 52 pounds, as the swelling disappeared.

The present illness began on February 26, 1938 with typical bronchopneumonia which cleared up within a reasonable length of time in another hospital. The convalescence was complicated by thrombosis in both arms and legs, edema, and fever. Because of this and annoying palpitation, the patient was transferred to Eppinger's clinic by ambulance from bed to bed.

The heart and lungs were normal on physical and roentgenographic examinations. Only sinus tachycardia could be found by electrocardiography. Both legs showed signs of mild thrombophlebitis and edema. There was low grade fever. The urine

was entirely negative. The red blood cell count was 4,730,000; hemoglobin 75 per cent; white blood cell count 7480.

The patient was placed on the Raw Food Diet and was given luminal. Diuresis promptly occurred, reaching a peak of 2300 c.c. passed on the fourth day. In the course of a week, she lost about five pounds and the chart settled to normal.

This case is interesting in that the thrombophlebitis and its effects seemed to yield quickly to the Raw Food Diet after having smoldered along for weeks under treatment in the other hospital.

Case 4. A 59 year old woman was admitted on April 25, 1938, complaining of abdominal pain. Six months previously she had developed signs and symptoms of diabetes mellitus, which were readily controlled by diet without the use of insulin. Otherwise she had been well up to two weeks before admission, when she began to have boring pain in the right upper quadrant associated with nausea. She had been slightly jaundiced for three days.

Thorough study revealed that biliary obstruction was complete, and she was transferred to the surgical ward. The preoperative diagnosis was cancer of the head of the pancreas, but the postoperative diagnosis was hepatitis. The liver was found to be slightly enlarged, but of normal consistency and color. The gall-bladder, ducts, and surrounding tissues were edematous. There were no signs of gall-stones, metastases, or cirrhosis.

For the first three postoperative days she was given intravenous glucose alternating with physiologic saline. Each day she received at least 1000 c.c. of the latter, and total intravenous fluids to the extent of 2000 c.c. During the whole first week after the operation the urinary output was between 500 and 900 c.c. per day. The jaundice grew more and more marked, and the patient, sicker. Following medical consultation, the excessive sodium chloride intake was stopped. Within four days there occurred a spontaneous and dramatic diuresis, and the patient felt immediately better. She was soon transferred back to the medical service, where the Raw Food Diet was given until she was well along in convalescence.

This case serves to emphasize the deleterious effects of saline administrations to patients having inflammatory disease of the liver. The same may be said for similar disease of other organs. The principles of the Raw Food Diet are best applied to these cases. Incidentally, it might be pointed out again that this diet is rich in carbohydrate, which in itself is a desirable feature in the treatment of liver disease.

In addition to the last three cases just described I followed the effects of the Raw Food Diet on patients with active rheumatic fever, subacute bacterial endocarditis, nephrosis, pneumonia, and catarrhal jaundice. Since the first three of these five patients were chronically ill, various dietary régimes could be carefully studied for each and checked for results, one diet against the other. On the basis of such controlled experiments, which were similar to those outlined in the first two cases presented, the Raw Food Diet seemed regularly to promote improvement. I shall not go into the details, because each case was complicated by the use of other measures under investigation besides the diet. I can only report a favorable clinical impression derived from the use of the latter. The same impression must also suffice in appraising the Raw Food Diet as used in the remaining two cases, since it was pre-

scribed immediately on the admission of each patient and no control periods were feasible. The woman with lobar pneumonia was given quinine intramuscularly, pyramidon, and various stimulants besides the Rohkost Diät. By the fourth day her temperature was normal. The woman with catarrhal jaundice received only the Raw Food Diet, and within 10 days all tests were normal. Though numerous case reports, similar to the nine just described, have appeared in the foreign literature during the past few years, there are as yet no critical studies available in which a series of patients with a given disease has been treated with the Raw Food Diet and compared with a control group.

Comparison of the Raw Food Diet With Similar Diets. Some of you may be wondering just how this Raw Food Diet differs from other, more familiar diets like the "Vegetarian Diet," the "Salt-free Diet," and the "Gerson Diet." The first in question is easily disposed of, because it is not recognized in scientific circles. Each vegetarian has his peculiar eating habits and ideas, which may indeed be shared by others in cult-like fashion. Thus, there may be no positive reason for adhering to such a diet, but rather a faddy notion that it is wicked to eat meat, since it must be obtained by killing. The principal difference between the strict Vegetarian and the Raw Food Diets is that the former admits considerable cooking.

The "Salt-free Diet" [10] as used in kidney disease goes back to the work of V. Noordan in 1902. The practice of restricting salt intake as a means of producing diuresis was studied by Strauss in 1903 and the school of Widal in 1904. The man, however, who finally clarified this whole subject clinically was Volhard. According to him the Salt-free Diet should contain no more than one gram of NaCl in the food per day. The best exposition of Volhard's ideas on the Salt-free Diet that I could find, appeared in the section on the treatment of nephrosis in his 1918 monograph [11] on Bright's disease. He pointed out that most raw foods are poor in sodium chloride and, therefore, especially desirable. Worthwhile suggestions were made as to ways of making foods tasty with the use of plant principles like caraway, anise, poppy seed, parsley, dill, onion, and lemon. The chief difference between his recommendations in 1918 and those of Eppinger in 1939 is one of refinement. Volhard allowed more foods including milk, some meat and cheese, and more cooking. He was not concerned with potassium and vitamins.

The Gerson diet is commonly called the Sauerbruch-Herrmannsdorfer-Gerson Diet [12] or S.H.G.–D. This imposing name was assigned in order to give credit to the three men who in 1925 gave a symposium on the dietary treatment of severe forms of tuberculosis. Sauerbruch, a surgeon specializing in tuberculosis, persuaded Herrmannsdorfer to study the effects of diets on wound infection and wound healing. This led to Herrmannsdorfer's going to visit Gerson and bringing the latter back to Munich to continue their studies together. The diet is quite similar to the Raw Food

Diet in ruling out table salt and salty foods and emphasizing raw fruits and vegetables. But it also permits considerable cooking and allows up to three pints of milk daily and 500 grams of meats every week. The authors' conception is that in disease the physiological equilibrium of important ions is disturbed and can be restored through food. The special feature of the diet is considered to be the generous supply of all minerals except sodium. Gerson [13] has recently written that he regards the effects of the diet as unspecific and recommends it for a long list of diseases. Thus, the S.H.G.–D. becomes a kind of gun-shot measure and in this respect differs sharply from the Raw Food Diet whose purpose is simply to promote the excretion of sodium and to supply adequate amounts of potassium.

Sodium.[14, 15, 16] Since the Raw Food Diet is fundamentally a low sodium, high potassium one, it is proper now to discuss the metabolism of these minerals, even though cursorily. The average American consumes [14] and excretes about four grams of sodium or 10 grams of sodium chloride per day; the figures for Europeans tend to be considerably higher. The Na^+ ions constitute the largest fraction of the total base of the body fluids and play a major rôle in the osmotic relationships of these fluids. The sodium [15] content of the blood serum is normally 335 mg. per cent. Sweat [15] contains 0.7 per cent NaCl. Sodium is associated with water retention,[2, 17] but a healthy individual can ingest as much as 35 to 40 grams of the chloride [14] per day without accumulating interstitial fluid. The excess is excreted promptly in the urine, since the kidneys maintain the proper structure of the blood plasma. If a normal, average man is placed on a salt-free diet or starved, the excretion of sodium chloride is quickly curtailed in an apparent attempt on the part of the body to husband its supply.

Potassium.[14, 15, 16] The average daily intake of potassium is two to three grams. The K^+ ion is the principal cation within the tissue cells where it exists partly in some "bound" combination [14] with the complex phosphate anions, so that it is not freely ionized and hence cannot exert osmotic pressure apart from the whole molecule. For this reason, an ordinary increase in interstitial water does not affect the cellular potassium or water content. The potassium level of the blood serum is very constant at 19 mg. per cent.[15] When potassium chloride is ingested, both K^+ and Cl^- are excreted simultaneously in the urine, and none is stored in the intercellular fluid. Hence, potassium is considered diuretic in its effect on water balance. The pharmacological action [14] of potassium is to increase neuromuscular irritability.

Theoretical Indications for the Raw Food Diet. I should like again to emphasize that the Raw Food Diet is low in sodium and high in potassium. The use of this diet in various diseases in which sodium chloride and water are retained has already been described. There remains for discussion an additional number of possible indications for this therapeutic agent.

Kern [18] has recently written an interesting paper concerning the water balance in the clinical manifestations of allergy. According to his concept,

allergic "symptoms may be the result of the concerted action of two causes of edema, the one (allergenic) acting locally in the shock organ, the other a cause of generalized hydration." He regards the first factor as by far the most important of course, but points out that the second non-specific factor may be decisive in the sense of the last straw. Thus, an allergic reaction may be able to produce symptoms, only when fortified by some parallel condition which facilitates the production of edema through water retention. Such accessory mechanisms may be associated with the menses, with a fall in barometric pressure before a storm, and with diet. Theoretically, the Raw Food Diet should benefit certain allergic conditions by minimizing any tendency to generalized edema.

Another pertinent consideration has to do with Ménière's syndrome characterized by vertigo, tinnitus, deafness, nausea, and vomiting. Talbott and Brown [19] have concluded that gross retention of water and sodium chloride by the body is not the inciting agent in acute attacks. Still they recognized the merits of a low sodium diet in the treatment of this syndrome. They then argued that the effective principle in this diet might be the relative rather than the absolute amounts of sodium and potassium contained. On this basis they treated a series of patients with a normal diet to which was added from six to 10 grams of potassium chloride in aqueous solution daily. The results were favorable. It was admitted that the precise action of potassium chloride in this respect was not known but was believed to be concerned with diuretic effects. Thus, there is every indication for the use of the Raw Food Diet in Ménière's syndrome.

Other investigators who have stressed the importance of the sodium-potassium ratio are McQuarrie, Thompson, and Anderson.[20] In their studies concerning the effects of excessive ingestion of sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children they found that one part of potassium completely abolished the action of at least three chemically equivalent parts of sodium. A high NaCl intake caused a marked reduction in the degree of glycosuria and at the same time an elevation in both systolic and diastolic blood pressure. Potassium chloride exerted a diametrically opposite effect. These results would suggest that the Raw Food Diet is indicated in cases of spontaneous hypoglycemia, but contraindicated in diabetes mellitus.

In concluding this discussion of the theoretical indications for the Raw Food Diet, I should like to mention the pioneer work of Barker [17] who in 1932 described a method for treating cases of cardiac and nephrotic edema with an acid ash diet, in which a low ratio of sodium to potassium was maintained by the addition of potassium chloride. Finally, I call your attention to a paper by Rusk,[21] outlining a number of pathological conditions in which water retention is the prime factor. He developed the thesis that satisfactory dehydration depended on replacing lost serum proteins and rebalancing the sodium-potassium intake. The application of these principles was recom-

mended on the basis of his experience for, among others, migraine, urticaria, and obesity.

In speaking of these numerous and seemingly heterogeneous conditions from *allergy* to *obesity* I wish merely to suggest that there is reason to believe the Raw Food Diet might prove beneficial in selected cases. I do not imply, as Bircher-Benner [22] has, that it is of value for all diseases. Indeed, this diet might lead to serious consequences in Addison's disease and would contribute to heat cramps in an individual working under conditions of high temperature and low humidity.

A Design for the Raw Food Diet. In order to give you a working basis for the preparation of Raw Food Diets I have designed several tables which supply all the available, necessary information not commonly found in books on dietetics. A recent English compilation [23] proved invaluable as a source of figures for the sodium and potassium contents of the various foods. The vitamin values were taken from data [24] put out by the United States Department of Agriculture, Washington, D. C. I also acknowledge the expert help of Miss Helene Henley, Dietitian at Columbia Hospital, Milwaukee, in working out the details of these tables.

TABLE III

DIET OUTLINE

Breakfast	Household Measures
Fruit, raw, 12%	1 average serving
Bread, salt free, toasted	1 thin slice
Egg, cooked	1
Butter, salt free	1 square or 2 teaspoons
Marmalade or honey	2 teaspoons
Sugar	1 teaspoon
Tea, clear with lemon	As desired
Luncheon	
Vegetables, raw, 3%, 9%	1½ cups
Mayonnaise, salt free	1 tablespoon
Fruit, raw, 6%, 9%, 12%, 15%	1 average serving
Butter, salt free	1 square or 2 teaspoons
Sugar	1 teaspoon
Tea, clear with lemon	As desired
Tea	
Fruit, raw, 12%	1 average serving
Bread, salt free	1 thin slice
Butter, salt free	1 square or 2 teaspoons
Marmalade or honey	2 teaspoons
Sugar	1 teaspoon
Tea, clear with lemon	As desired
Supper	
Cheese	1 average serving
or	
Egg, cooked	2
Fruit, raw, 12%	1 average serving
Jelly or fruit preserves	2 teaspoons
Butter, salt free	1 square
Nuts	1 average serving
Sugar	1 teaspoon
Tea, clear with lemon	As desired

TABLE IV

SAMPLE MENU

Breakfast	Household Measures
Orange juice	½ cup
Egg, coddled	1
Toast, salt free	1 thin slice
Butter, salt free	1 square or 2 teaspoons
Honey	2 teaspoons
Sugar	1 teaspoon
Tea, clear with lemon	As desired
Luncheon	
Celery hearts	2 average hearts
Carrot sticks, raw	1 large carrot
Vegetable salad, raw	
Tomato	1 medium tomato
Sliced cucumbers	¼ cup
Lettuce wedge	⅛ head lettuce
Mayonnaise	1 tablespoon
Strawberries, fresh	½ cup
Sugar	1 teaspoon
Butter, salt free	1 square or 2 teaspoons
Tea, clear with lemon	As desired
Tea	
Fresh grapefruit sections	½ cup
Toast sticks, salt free	1 thin slice
Orange marmalade	2 teaspoons
Butter, salt free	1 square or 2 teaspoons
Sugar	1 teaspoon
Tea, clear with lemon	As desired
Supper	
Jelly omelet	
Eggs	2
Jelly	2 teaspoons
Fresh pineapple, shredded	½ cup
Sugar	1 teaspoon
Butter, salt free	1 square or 2 teaspoons
Almonds, shelled whole	¼ cup
Tea, clear with lemon	As desired

KEY TO THE FOOD CHARTS

Initials following food items:

F. O.	Flesh only	L. O.	Lean only
F. S.	Flesh and skin	L. F.	Lean and fat
K. O.	Kernel only	s.s.s.	Stewed without sugar

Vitamin A is designated in international units.
Vitamin B_1 is designated in micrograms of thiamin.
Vitamin C is designated in milligrams of ascorbic acid.
Vitamin D is designated in international units.
Vitamin G is designated in micrograms of riboflavin.

[1] Vitamin values are for uncooked products unless otherwise indicated.

* Values refer to 100 grams of raw weight corrected for vitamin losses in cooking.

(X) Food has been tested and found lacking in this vitamin, or the quantities present are insignificant.

— No reliable value can be given.

< Less than.

In table 3 you will recognize the diet used in Eppinger's clinic already outlined in table 2, with household measures added. Table 4 is more specific in naming the articles of food, whereas table 5 gives all the pertinent data as to their compositions. To recapitulate, I should like to point out the low sodium-high potassium ratio, and the low protein and caloric content. For this particular diet, the vitamin A and C values are over twice the average requirement; B_1 and G, about half the average requirement; and vitamin D is conspicuously lacking.

TABLE V

Nutritive Value of the Sample Menu in Table 2

Food	Household Measure	CHO	Pro.	Fat	Calories	Na mg.	K mg.	A I.U.	B_1 Mic. gm.	C mg.	D I.U.	G Mic. gm.
Orange juice	½ cup	12.00	.6	—	50	1.70	179.0	250	107	38	(X)	—
Bread, saltless, white	2 average slices	21.20	3.6	0.8	103	35.00	46.0	(X)	25	(X)	(X)	12
Eggs	3	—	18.0	18.0	234	202.50	207.0	1020	180	—	60	690
Butter, saltless	4 squares	—	—	34.0	306	25.00	6.0	1040	(X)	(X)	(X)	(X)
Jelly	2 teaspoons	10.00	—	—	40	2.52	2.5	—	—	—	—	—
Honey	2 teaspoons	10.00	—	—	40	1.09	5.1	—	—	—	—	—
Marmalade, orange	2 teaspoons	12.00	—	—	48	1.82	4.4	—	—	—	—	—
Sugar	5 teaspoons	25.00	—	—	100	0.10	0.50	—	—	—	—	—
Celery hearts	2 average	1.5	.5	—	8	68.50	139	—	17	4	(X)	17
Raw carrot sticks	1 average carrot	9.0	1.0	—	40	95.00	224	10,000	70	8	(X)	67
Tomato, raw	1 average	3.00	1.00	—	16	2.80	288	1150	75	27	(X)	52
Cucumbers	¼ medium or ½ cup	2.20	.7	—	12	6.50	70	(X)	27	5	(X)	22
Lettuce wedge	¼–4″ head	1.10	0.60	—	6	1.50	104	125	42	10	(X)	50
Mayonnaise	1 tablespoon	.40	.20	11.2	103							
Fresh strawberries	½ cup	6.00	1.00	—	28	1.50	161	50	20	87	(X)	—
Grapefruit	½–4″ diameter or ½ cup	9.00	1.00	—	36	1.30	234	(X)	70	40	(X)	—
Fresh pineapple	½ cup diced	12.00	.4	—	50	1.60	247	200	90	25	(X)	25
Almonds, shelled	¼ cup	1.07	5.10	16.70	106	1.90	285	(X)	82	—	(X)	—
	Totals:	135.47	33.7	80.7	1326	450.33	2202.5	13,835	805	244	60	935

Finally, there is presented in table 6 a list of raw foods, carefully selected on the basis of low Na-high K content, which may well be used in planning individualized diets. The figures for carbohydrate, protein, and fat fractions are not given, because they are so easily obtained in standard manuals. The household measures, sodium, potassium, and vitamin values will be especially helpful to anyone of you interested in doing investigative work. For the therapeutic application of the Raw Food Diet, however, the practicing physician need merely limit his prescriptions to foods on this list.

SUMMARY

1. The considerable lay and commercial interest in the dietary use of raw plant-products is discussed.

2. The scant medical attention given to this subject in this country is scored.

3. Eppinger's concept of the therapeutic value of the Raw Food Diet is reviewed.

4. The clinical application of this principle in nine cases is described in varying detail.

5. The Raw Food Diet is compared with other similar diets.

6. Theoretical indications for this diet are advanced.

7. Tables are presented to aid physicians in the planning of individualized Raw Food Diets.

TABLE VI

RAW FOODS

(low in Na; high in K)

Food Items	Household Measure	Mg. per 100 gm.		Vitamin Values per 100 Grams[1]				
		Na	K	A I.U.	B_1 Mic. gm.	C mg.	D I.U.	G Mic. gm.
Fruits:								
Apples (F. O.)	⅔ of 2¾″ diam., or 1, 2″ diam.	2.0	120	50–100	18–69	3–6	(X)	30–73
Apricots, fresh	2, 1⅞″ diameter	<1.0	320	4,000	60	6	(X)	88
Apricots, dried	½ c. packed or 16 small halves	56.4	1,880	5,800	171	—	—	57
Avocado pears	1, 2″ long	16.0	396	128	100	28	(X)	—
Bananas	1, 6½″ long or ¾ c. sliced	1.2	348	400	55	2–28	0	35–48
Blackberries	1⅓ cups	3.7	208	80	<25	—	(X)	30
Blueberries	¾ cup			100	45	6	(X)	—
Cherries	¾ cup	2.8	275	(X)	50	3–5	(X)	—
Cranberries	1 cup	1.8	119	70	—	19	0	—
Currants, black	¼ cup	2.7	372	—	0–60	230	(X)	—
Currants, red	¼ cup	2.3	275	120	30–60	25	(X)	—
Currants, white	¼ cup	1.5	291					
Currants, dried	¼ cup	19.5	708					
Dates	4 dates	4.8	754	66–83	70	0	0	30
Figs, green	3½″ diameter	1.6	268	—	57	1.8–8.7	(X)	—
Figs, dried	17 figs	86.7	1,010	115	300	—	(X)	—
Gooseberries, green	½ cup	1.9	210	380		21		
Gooseberries, ripe	½ cup	1.2	170			39		
Grapes, black (F. O.)	½ cup	1.7	316	(X)	45	4	(X)	24
Grapes, white (F. S.)	½ cup	1.6	250	(X)	45	4	(X)	92
Grapefruit (F. O.)	½ cup	1.3	234	(X)	70	40	(X)	—
Lemons, whole	1 lemon	6.0	163					
Lemon juice	½ cup	1.5	142	(X)	18	60	(X)	3
Logan berries	1⅛ cups	2.5	257					
Melons, cantaloupe (F. O.)	¼ of 4½″ melon or ½ c. pulp	13.5	319	2,390	57	30	(X)	—
Mulberries	¾ cup	2.1	257					
Nectarines	1 medium nectarine	9.1	268					
Oranges (F. O.)	Pulp of orange 2½″ diam.	2.9	197	50–250	78	30°–60°	(X)	27.8
Orange juice	½ cup	1.7	179	50–250	107	38°	(X)	27.8
Peaches, fresh (F. S.)	1 medium	2.7	259	(X)–1670	30–120	1–17	(X)	65
Peaches, dried	1⅓ cups	6.0	1,100	3,400	—	—	—	—
Pears (F. O.)	1 medium	2.3	127	(X)	20–54	3.8–10	(X)	76
Pineapple, fresh (F. O.)	½ c. diced, 2 slices 2½×¾″	1.6	247	200	90	20–60	(X)	25
Plums, (F. S.)	3–1½″ diameter	1.7	188	360	50	2–8	(X)	40
Prunes, dried	12 prunes	12.2	864	1,560	180	(X)	—	—

[1] Values per 100 ml.

TABLE VI—*Continued*

Food Items	Household Measure	Mg. per 100 gm.		Vitamin Values per 100 Grams[1]				
		Na	K	A I.U.	B_1 Mic. gm.	C mg.	D I.U.	G Mic. gm.
Quinces	3–1½" diameter	3.2	203					
Raisins, dried	¾ cup	52.2	860	(X)	105	0	—	98
Raspberries, red	1 cup	2.5	224	130	<25	25	(X)	—
Strawberries	¾ cup	1.5	161	50	<25	52–87	(X)	—
Tangerines (F. O.)	2–2" diameter	2.2	155	350	120	26	(X)	—
Nuts:								
Almonds (K. O.)	¾ c. or 10 nuts	5.8	856	(X)	246	—	(X)	—
Brazil nuts (K. O.)	¼ cup	1.5	760		1,020			
Chestnuts (K. O.)	25–30 nut meats	10.9	497		270			
Coconut, fresh (K. O.)	½ cup	16.5	436		30	1–3		
Peanuts (K. O.)	½ cup	5.6	680	(X)	1,050	9.8	(X)	460
Walnuts (K. O.)	1 cup	2.7	687	40	340	20	(X)	—
Vegetables:								
Beans, lima	½ cup	61.5	1,700		340	36	(X)	—
Beans, snap	⅔ cup	43.2	1,160	2,000*	45*	18	(X)	240
Cabbage, red	1½ cups	31.6	302	40	—	57.3	(X)	—
Carrots, old	1 large carrot	95.0	224	10,000*	70*	8	(X)	67
Celery	4 med. stalks or ¾ c. cut	137.0	278	0	35	8	(X)	35
Chicory	2½ cups	7.3	182		30–75			20–30
Cucumber	½ c. sliced or 3"×1¾" diam.	13.0	141	(X)	55	10	(X)	44
Eggplant	Sliced 4½×½" or ½ c. diced	2.5	238	25	60	2	(X)	31
Endive	2–4 stalks or ½ head	10.1	381	3,850	100	12	(X)	61
Horseradish	½ cup, scant	7.9	579			122		
Lentils	3 cups	36.0	673	<100	630	3	(X)	—
Lettuce	¼–4" head or 16 leaves	3.1	208	200–300	85	20	(X)	100
Onions	½ c. or 3, 1½" diam.	10.2	137	0	24	9	(X)	123
Onions, spring	20, 5" long	13.0	226					
Parsnips	½ cup diced	16.5	342	(X)	115	32	(X)	—
Peas, fresh	¾ cup	0.5	342	700*	390*	25	0	150
Peas, dried	½ cup	37.9	985	530*	1,440	—	(X)	800
Pumpkin	1½ cups	1.3	309	1,200*	—	6	(X)	35
Radishes	10, 1" diameter	59.0	240	(X)	39	26	(X)	35
Tomatoes	1, 2½" diameter	2.8	288	1,150	75	27	(X)	52
Turnips	1 medium	58.0	238	0–40	33	25–50		40
Watercress	40 sprigs–3 cups	60.0	314		180	60	(X)	85
Olive oil	1 cup	0.1	Trace	1,000			(X)	

CONCLUSIONS

The cardinal feature peculiar to the Raw Food Diet as described above is its low sodium-high potassium ratio. Thus, the diet is of value in cases exhibiting retention of sodium chloride and water. Though such benefit has actually been demonstrated for relatively few diseases, there is every indication that more may properly be added to the list. The Raw Food Diet is not suitable for extended use nor for healthy individuals, because of certain inherent deficiencies.

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CASE REPORTS

ERYTHROBLASTIC ANEMIA OF THE ADULT*

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THE circulating blood of normal adults rarely contains nucleated members of the erythrocyte series. The megaloblast, erythroblast, pronormoblast and normoblast are normally retained in the bone marrow until fully matured before released.

In certain diseases, however, the immature forms may make their appearance in the circulation. The megaloblast occasionally is found in myelogenous leukemia, macrocytic anemias, lead poisoning, or other anemias associated with rapid cell formation.[1] The erythroblast may be found in the blood of normal new born infants during the first five days of life and is also found in the same diseases enumerated for the megaloblast.[1] Pronormoblasts may be found in the circulation in all anemias associated with rapid cell regeneration, including familial hemolytic icterus, sickle cell anemia, anemia of acute hemorrhage, lead poisoning, and in macrocytic and myelophthisic anemias.[1] Normoblasts have occasionally been seen in the blood of apparently normal individuals and they are found in all the anemias previously mentioned, but they are absent, of course, in aplastic anemia.[1]

Any anemia characterized by large numbers of nucleated red cells in the circulating blood may be called an "erythroblastic anemia," using the term "erythroblast" in the broader sense of the word to denote immaturity of the red cell rather than a specific cell type. When the nucleated red cells are also associated with an increase in immature white cells this condition may be known as a "leuko-erythroblastic anemia."[2] Other names which have been applied to clinical entities of this category are erythroblastemia, pseudoleukemia, erythroleukemia, erythroleukosis, leukanemia, erythroblastosis, megaloblastic anemia and leuko-erythroblastosis.[3]

In children, there appear two examples of this type of anemia, the Cooley's or Mediterranean anemia, the origin of which is obscure, and the disease called "erythroblastosis fetalis" or erythroleukoblastosis.[4] It has recently been shown that the latter may be the result of a reaction to anti Rh agglutinins present in the maternal blood.[5, 6] These both appear unassociated with any other disease and are characterized by large numbers of immature erythrocytes and granulocytes in the circulating blood and by splenomegaly. Rare cases of Cooley's anemia surviving to adulthood are reported,[7] but erythroblastosis fetalis is either fatal or is cured in infancy.

In adults, on the other hand, the presence of an erythroblastic blood picture

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is usually associated with, or secondary to, some other disease.* The diagnosis of "erythroblastic anemia" in the adult should not be considered as a final diagnosis but only as a working diagnosis until the true nature of the disease process makes itself known. Some of the conditions which have been reported as producing or accompanying an erythroblastic blood picture are:

1. Excessive exposure to roentgen-ray or radioactive material.
2. Chemical or drug poisoning.
3. Malignancy with metastases to bone marrow.[9]
4. Chronic diarrhea, as found in rickets, scurvy or steatorrhea.
5. Recurrent and severe hemorrhage.
6. Chronic or severe infections.
7. Malformation of the circulatory system, such as congenital heart disease or arteriovenous aneurysms.
8. Hemolytic anemias.
9. Extra medullary hemopoiesis (associated with enlargement of liver and spleen).
10. Myelogenous leukemia.
11. Multiple myeloma.
12. Myelosclerosis and myelofibrosis of obscure etiology.[10]
13. Marble bone disease of Albers-Schonberg.
14. Polycythemia.[11]
15. Agnogenic myeloid metaplasia of the spleen.[12, 13]

In this paper we are presenting a case of erythroblastic anemia in an adult female. This case illustrates the difficulty in diagnosis which this blood picture may cause and the necessity of searching for a causative factor.

Case Report

E. M., a 45 year old white housewife, was first admitted to St. Luke's Hospital on March 12, 1939 and returned on four subsequent admissions before her death on December 28, 1939. Her chief complaint on admission was weakness and menorrhagia. Her menses had been normal until the February period, which came five days early. There was a profuse flow for several days and this was followed by severe headaches and a temperature of 102° F. She had noticed progressive weakness, and her family had noticed some pallor and jaundice. There was shortness of breath on exertion. Her past history was negative except for influenza in 1918. Her father had died at the age of 52 of carcinoma of the liver. Her mother and siblings are living and well. Her husband and four children are living and well.

Physical examination showed an acutely ill white female with a slight icteric color to the skin and sclerae. There were no palpable lymph glands. The heart sounds were normal. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The lungs were normal. The liver and spleen were not palpable. There were no pathological neurological signs and no other physical abnormalities of note.

Roentgenograms of the chest, gastrointestinal tract, gall-bladder, kidneys and long bones were all normal.

Laboratory findings: Urinalysis, phenolsulfonphthalein excretion and Mosenthal test were normal. Gastric analysis showed the presence of a normal amount of free and total acid. Blood examination showed negative Wassermann reaction,

* We know of only one reported case of chronic pure erythroblastic anemia in the adult.[8]

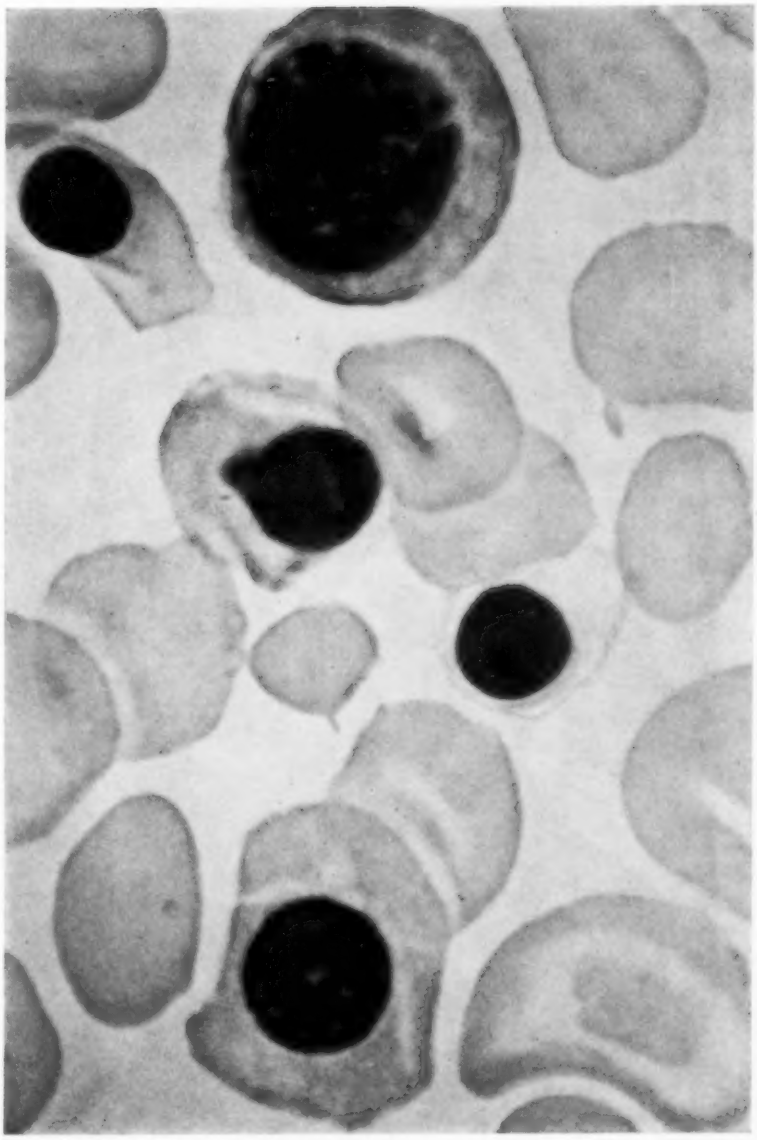

FIG. 1. Blood smear on admission showing erythroblasts, pronormoblasts, and normoblasts. Magnification × 920.

icterus index 22, urea N 7.9 mg. per cent, sugar 92 mg. per cent. Van den Bergh reaction was positive indirect. Fragility test showed hemolysis starting at .46 per cent and complete at .36 per cent.

Hematologic findings: Red blood cells 1,300,000, hemoglobin 44 per cent (Sahli), nucleated red blood cells 2,700, white blood cells (corrected for nucleated red blood cells) 3,700, platelets 17,400. Examination of the blood smear showed polychromatophilia of the red blood cells. Many megaloblasts, erythroblasts and normoblasts were present (figure 1). There were an unusual number of smudged cells, but no abnormal white cells were seen.

The subsequent hematologic findings are represented graphically in figure 3.

Sternal marrow biopsy showed 146 nucleated red cells to 100 white blood cells, or a ration of 6 to 4 (normal value 4 to 6). The granulocytes showed a pronounced shift to the left, and a number of primitive stem cells were seen.

Course: The patient was given repeated blood transfusions and extensive liver and iron therapy without good results. On May 16 the spleen could first be palpated. With the low platelet count it was felt that we might now be dealing with a thrombocytopenic purpura so that splenectomy was recommended. After irradiating the spleen with 450 "r" units it was removed on May 31. There was slight clinical improvement. However, about two months later, there was a return of menorrhagia. It was decided to treat this symptom by producing an artificial menopause. Accordingly, she was given 2,240 "r" units to the pelvis in September through four fields and her menses stopped. Her course was then marked by complaints of weakness and soreness of her gums, which became progressively worse, and which were resistant to therapy. Blast cells now appeared in the circulation (figure 2), and the true diagnosis of acute myelogenous leukemia was now suspected. The teeth became loose in the sockets, and pus could be expressed from around the gum margins. She was readmitted for blood transfusions and followed in our dispensary until her final admission on December 13, 1939, at which time she showed a progression of pyorrhea and gingivitis. She had developed an abscess of the buttock from which gram negative bacilli were cultured. The liver could now be palpated six fingers'-breadth below the costal margin. The right knee became inflamed and painful on motion. In spite of repeated transfusions the patient became progressively weaker and died on December 28, 1939, eleven months after the onset of her disease.

An attempt was made to examine the cells clustered in the spleen by injecting 1 c.c. of 1 to 1,000 adrenalin intramuscularly, and studying the peripheral blood at the end of 15, 30 and 45 minutes. The first adrenalin study was done on the fourth day of her admission to the hospital. After the injection of adrenalin it was noted that the total leukocyte count rose from 3,800 to approximately 14,900, an increase of about 350 per cent. There was only a slight increase in the number of erythrocytes.

The procedure was repeated again two days after the splenectomy. At this time although the white count did not go so high as the first time there was, nevertheless, slightly more than 100 per cent increase. There was also a 25 per cent increase in the total number of erythrocytes. More striking was the marked increase in the total number of platelets which rose from 17,000 to 102,000 per cu. mm.

Nucleated red cells also increased, following the injection of adrenalin, about 250 per cent. The reticulocytes also increased by about one-third the total number. At this time there appeared in the peripheral blood large numbers of cells which could not be classified. There were small and large mononuclear cells with no apparent nuceoli and with only a small rim of cytoplasm. The primitive stem cells and the smudges did not increase appreciably over the percentage noted prior to the injection of adrenalin. A third similar examination was made on June 21, 21 days after the splenectomy. At this time there was a definite increase in the total number of white cells from two to three times the original figures. Prior to splenectomy it was as-

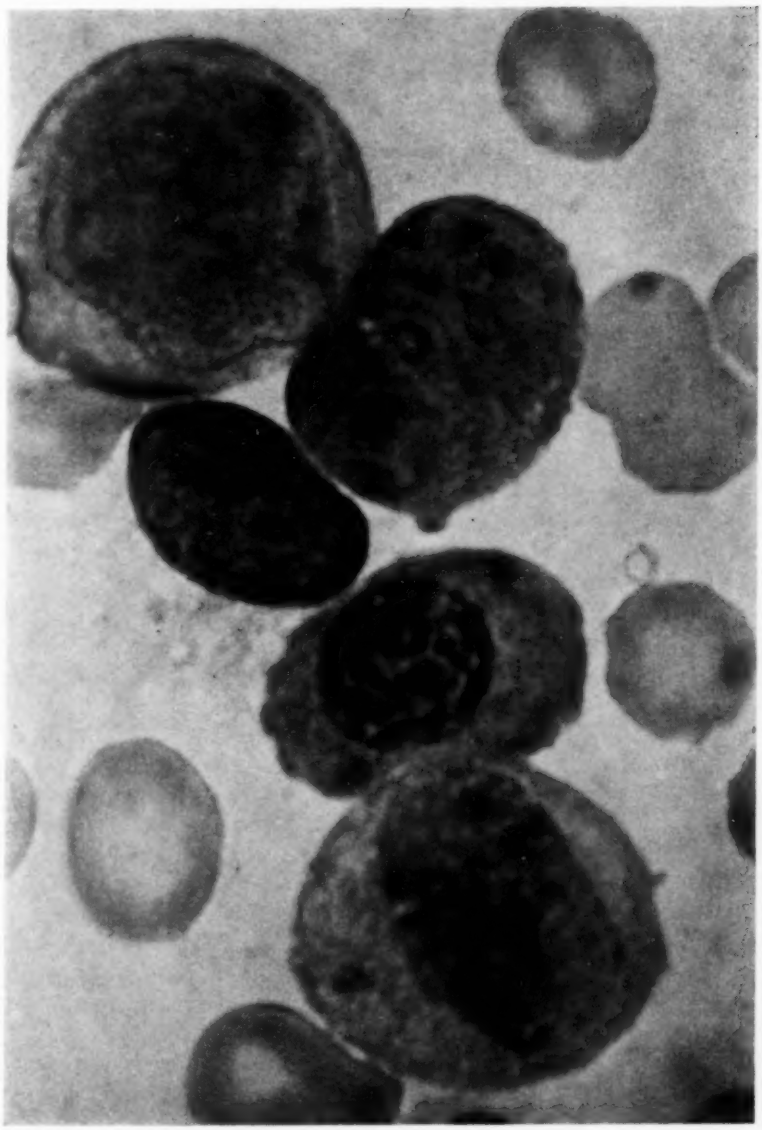

FIG. 2. Blood smear six months after admission showing several myeloblasts and one erythroblast. Magnification × 920.

sumed that the cells that appeared after the injection came entirely from the spleen. It must now be concluded that there must be another source from which these cells are squeezed out on the injection of adrenalin. The total erythrocyte count did not change materially. The total platelet count, the nucleated erythrocytes, and the reticulocyte count increased only slightly. Examination of the same smears revealed no significant change in the total number of primitive cells and smudges.

Pathological findings: The spleen, which was removed seven months before death, weighed 460 grams. Microscopically it showed many nucleated red blood cells lying between the venous channels and within the blood vessels. There was a small number of immature white cells seen which contained oxidase positive granules.

An autopsy was performed by Dr. Reuben Strauss,* one hour and 15 minutes after death. A small supernumerary spleen was found measuring 2 cm. in diameter. This showed a strikingly different microscopic picture from the spleen, for the architecture was now entirely obliterated by a diffuse infiltration of leukemic cells.

The liver weighed 3,070 grams. Cut sections showed diffuse infiltration with leukemic cells. Sections of bone marrow from the sternum and long bones showed replacement of marrow by leukemic cells. The remainder of the autopsy findings were characteristic of and consistent with the diagnosis of acute myelogenous leukemia.

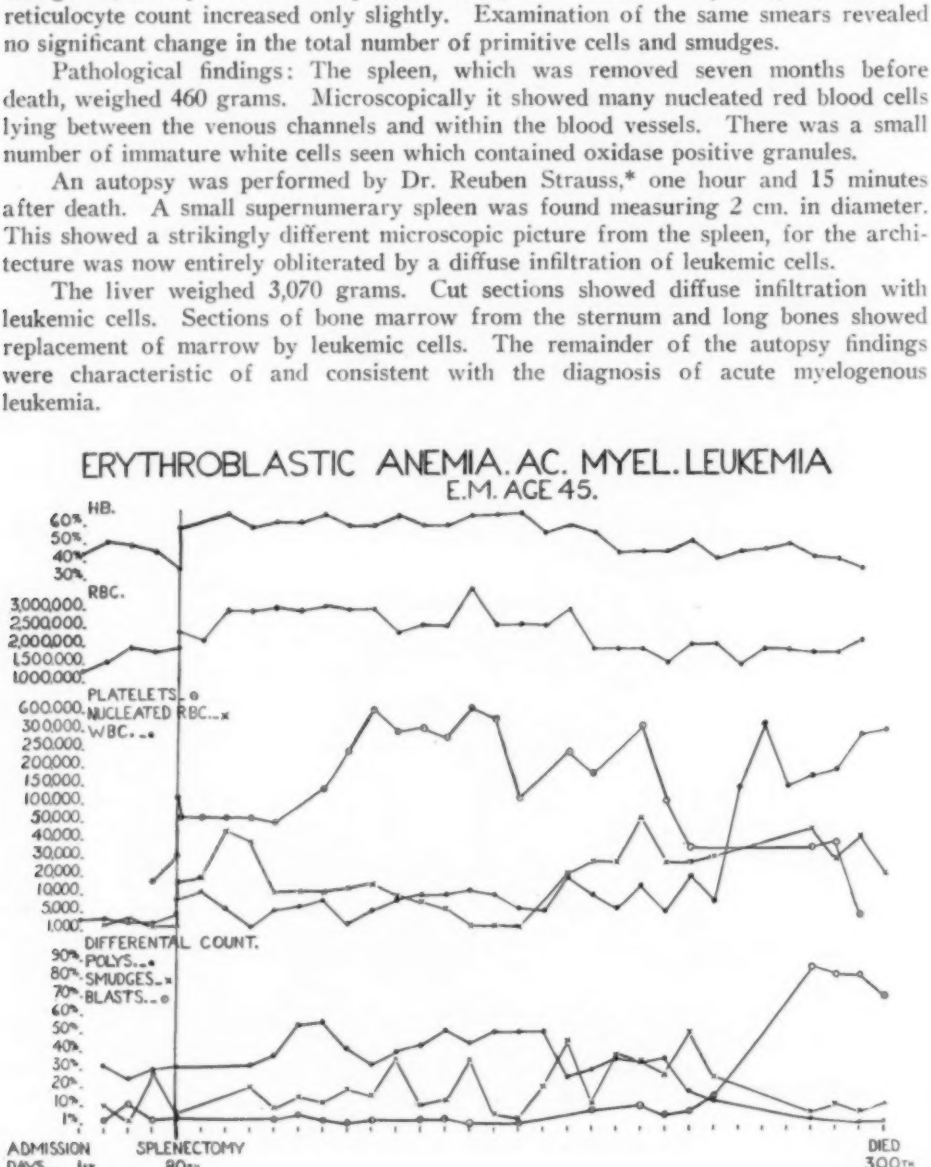

FIG. 3. Graph showing hematologic course. Following splenectomy note sharp rise in elements of erythrocyte series. Four months later sharp rise in total leukocyte count and myeloblasts with accompanying decrease in other cellular elements.

* I am indebted to Dr. Reuben Strauss for valuable aid in the preparation of this paper.

Comment

This case presented a diagnostic problem early in the course of the disease before the large numbers of myeloblasts made their appearance. However, the blood smears examined early in the course of this disease showed an unusual number of smudges of nuclear material which were impossible to identify. The granulocytes were decreased and showed increased basophilia and abnormal granules. This could be interpreted as demonstrating bone marrow hyperplasia and irritation. The presence of the large number of smudges was suggestive of acute leukemia even when no blast cells could be identified.

The sternal marrow demonstrated the presence of blast cells and added further weight to the diagnosis of leukemia. The total white blood cell count and the number of blast cells in the circulation, however, stayed low until the end of the ninth month of the disease when there was a sudden dramatic rise (figure 3).

The splenectomy was followed immediately by a sharp rise in all the blood elements, but most marked in the erythrocyte series (figure 3). The spleen is a regulating organ of the peripheral circulating elements, and this is a demonstration of what can happen when its inhibiting effect on hemopoiesis is released. Furthermore, the spleen is of value in the control of the white cell count in leukemia and splenectomy is, therefore, contraindicated. It is interesting to note that in this case the total white cell count did not rise significantly for four months after splenectomy.

Summary

Erythroblastic anemias in the adult are usually secondary to some other disease. A case is presented which at the onset presented the picture of a progressive refractory anemia with a marked erythroblastic response. Occasional myeloblasts were later found in the bone marrow and circulating blood, but the total white cell count remained within normal limits for several months.

Following splenectomy, which was performed in an effort to control bleeding, there was an immediate rise in the elements of the erythrocyte series. Clinical improvement followed, but four months after splenectomy there was a sharp rise in the total white cell count and the myeloblasts in the peripheral blood, which was accompanied by a decrease in the other cellular elements. The patient then ran a rapidly downward course typical of acute myelogenous leukemia and died on the three-hundredth day of observation. Autopsy findings confirmed the clinical diagnosis of acute myelogenous leukemia with an erythroblastic bone marrow response. This terminology is preferable to the older nomenclature which might have labeled this case "leukanemia," "erythroleukemia," or "erythroleukosis."

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INTERMITTENT CLAUDICATION RELIEVED BY THYROIDECTOMY; A CASE REPORT *

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AN analogy has been frequently drawn between angina pectoris and intermittent claudication. Indeed much evidence has been brought forth to show that the pain is produced by a similar mechanism which in the former affects the blood supply of the heart, in the latter that of the extremities.[1, 2, 3]

Wholey,[4] in a case report, states: "As an example of a mechanism similar to that of intermittent claudication, we can mention the attacks of angina pectoris with its diseased coronary arteries."

Heitz [5] reported 12 cases of intermittent claudication coexisting with angina pectoris.

Stroud and Shumway [6] sum up this relationship very clearly by stating: "Although the theory of 'coronary spasm' as the cause of angina has been discarded, and the fact is also recognized that pathology of the peripheral vessels does not necessarily indicate important pathology of the vessels supplying the brain, heart or kidneys, yet it does seem possible and even logical to expect some relationship between the physiologic and pathologic processes which will produce anoxemia in the calf or the muscles of the foot or toes, and those which will produce a temporary anoxemia to a part of the myocardium (angina pectoris) or a relatively permanent anoxemia to a portion of the myocardium (coronary occlusion)."

Landis [6] and Wright [6] have expressed similar views.

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From the Medical Department of the Jewish Hospital, Philadelphia.

There are moreover many case reports in the medical literature in which thromboangiitis obliterans, intermittent claudication and coronary thrombosis have occurred concurrently.[7, 8, 9, 10, 11, 12, 13]

It is the purpose of this report to present a case which gives further evidence of the intimate relation between these two conditions and at the same time points to the possibility of the further application of thyroidectomy as a therapeutic procedure.

Case Report

L. S., a gasoline station attendant, age 59, was admitted to the Jewish Hospital on the medical service of one of us (J. C. D.) on June 10, 1939.

The family and past medical history were essentially negative. The patient stated that for three months previous to admission he had suffered, on walking, severe cramping pains in the calf muscles of the right leg. This pain always occurred after walking exactly the same distance and would be relieved completely by a few minutes' rest. Its severity had been increasing in the past two weeks.

The heart was normal to physical examination. Its rate was 72 per minute, its rhythm and force regular. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic in both arms. The lungs and abdomen were negative. There were no glandular enlargements, tremor or nervousness. Neither the dorsalis pedis nor the posterior tibial arteries were palpable in either leg. There was a poor histamine response in both legs from above the knee downward, especially on the right. Oscillometric readings were as follows:

	Right	Left
Above Knee	3.00	5.0
Below Knee	1.00	4.0
Ankle	0.25	1.5
Foot	0.0	0.25

The urine was negative, the blood count was normal, and the blood sugar and the blood urea were 115 and 23 mg. per 100 c.c. of blood respectively. A glucose tolerance test showed a diabetic type of curve, rising to 280 mg. after one hour, and to 300 mg. per 100 c.c. at the end of two hours.

The patient was placed on a treatment routine consisting of Buerger's exercises, intravenous sodium chloride, histamine iontophoresis, and the use of a Pavex boot. With this therapy there was some slight improvement. He could walk a little further without pain than formerly and after two weeks he was sent home.

Treatment was continued in the form of intravenous sodium citrate, administered two and three times weekly, tissue extract hypodermically, histamine iontophoresis, and passive vascular exercise. Despite this routine, however, when the patient returned to work even after months of treatment he was unable to walk more than two blocks without pain.

On June 13, 1940 he was readmitted to the hospital with the history of increasing shortness of breath, palpitation, nervousness, fatigue and diarrhea during a period of six weeks previous to admission. The cramp-like pain in the right leg on walking had steadily increased in severity.

Examination revealed the presence of a soft movable mass in the right thyroid region. The heart was slightly enlarged to the left and there was a complete irregularity in its rate, force and rhythm. The blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram showed auricular fibrillation and myocardial degeneration, probably on an arteriosclerotic basis. The basal metabolic rate was plus 52.

Oscillometric readings, saline absorption and histamine flare tests showed about the same circulatory deficiency in both legs as on the previous admission.

He received four roentgen-ray exposures to the thyroid region after which he was sent home to await the results, if any, of this treatment. The mass in the neck, however, grew steadily larger and the thyrotoxic state worse. This result was in keeping with the findings of Friedman and Blumgart,[14] Pfahler and Vastine.[15] Others [16, 17, 18] have reported better results.

During this time the pain in the legs was unaltered.

On July 20, 1940 he was admitted to the surgical service of Dr. N. S. Rothschild. A large adenoma of the right upper pole of the thyroid gland and a smaller adenoma of the right lower pole, along with a cyst of the isthmus were found and removed. The pathological report was thyroid hyperplasia.

Recovery was uneventful, and after two weeks the patient was sent home with the loss of all of his thyrotoxic symptoms, including the auricular fibrillation. A basal metabolism taken at this time was —11.

He returned to his occupation and usual activities and was soon pleasantly surprised to note a complete loss of the former pain and disability on walking. Whereas formerly the pain had been of such severity as to force him to stop after two blocks, now he could walk for squares without the slightest discomfort in the legs and this despite the fact that all the treatments previously employed had been discontinued.

On examination of the extremities a year following operation, a faint dorsalis pedis arterial pulsation was detected. Nevertheless, at no time since the thyroidectomy has there been any suggestion of a return of the formerly disturbing intermittent claudication.

This patient recently was seen by one of us (AA) and has had no return of his intermittent claudication.

Comment

The association of hyperthyroidism and angina pectoris has been recognized for some years. Hirschfelder,[19] Mackenzie,[20] Sturgis,[21] Lev and Hamburger,[22, 23] Levine and Walker [24] have all noted this. More recently many reports have appeared concerning the successful use of subtotal or complete ablation of the thyroid gland for the relief of angina pectoris and congestive heart failure.[25, 26, 27, 28, 29, 30, 31, 32] The rationale behind this procedure has been the lowering of the metabolic rate to a point consistent with the ability of the heart to do its work without suffering embarrassment from the ischemia produced by diseased coronary arteries.[25] At the lowered metabolic level the demand of the heart muscle for oxygen is lessened; hence, what had previously been an inadequate circulation now becomes adequate. It is simply an application of the law of supply and demand. This occurs despite the fact that with the relief of a hyperthyroid state or production of a hypothyroid state where the gland is normal, the blood velocity is slowed.[33, 34] The oxygen demand has now been decreased to a point where even though the blood velocity is lessened, the blood supply is more than ample to care for the cardiac requirements. Hence, in effect, a cardiac reserve has been established.

This seems to have been precisely the course of events in our case. Instead of a cardiac reserve we here produced a 'tissue reserve" which allowed the patient greater freedom of action without disproportion between the oxygen supply and oxygen demand of the muscles of the leg.

Pickering and Wayne [1] have suggested that the stimulus which produces the pain of intermittent claudication and angina pectoris is an accumulation of

metabolites normally removed by oxidation in the tissue spaces. Hence, the essential factor in the production of this type of pain is a diminished oxygen supply to working muscles.

It seems reasonable then to suspect that if a lowered metabolism can decrease the oxygen demand of working heart muscle, it can have a like effect in the case of the muscles of the leg. Therefore, by lowering the oxygen demand of calf muscles the level at which pain begins can be raised so that oxygenated blood can be supplied in sufficient quantity to meet the normal demands of the individual.

Another explanation is found in the work of Eppinger and Levine.[35] They injected five patients previous to thyroidectomy with adrenalin producing typical anginal attacks. After operation, similar injections failed to produce any pain. They suggest that this alteration of response of the cardiovascular system to adrenalin may in a measure be responsible for the relief of the anginal pain. Similarly it may account to a certain degree for the relief of pain in this patient.

Conclusion

It seems surprising in view of the frequent association of angina pectoris and intermittent claudication, and of the numerous thyroidectomies performed specifically for the relief of the former condition that no statement has been made at any time in the literature of an associated relief of intermittent claudication. We believe that this is the only such case to be reported.

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31. Kennedy, W. R.: Treatment of congestive heart failure and angina pectoris by the complete removal of the normal thyroid gland, Canad. Med. Assoc. Jr., 1934, xxx, 610–614.
32. Altschule, M. D., and Volk, M. C.: Therapeutic effect of total ablation of normal thyroid on congestive failure and angina pectoris, Arch. Int. Med., 1936, lviii, 32–44.
33. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies on the velocity of the blood flow: xiv. The circulation in myxedema with a comparison of the blood flow in myxedema and thyrotoxicosis, Jr. Clin. Invest., 1930, ix, 91–106.
34. Kvale, W. F., and Allen, E. V.: Rate of circulation in the arteries and veins of man, Am. Heart Jr., 1939, xviii, 519–536.
35. Eppinger, E. C., and Levine, S. A.: Effect of total thyroidectomy on response to adrenalin, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 485–487.

EDITORIAL

ANDROGENS FOR ANGINA

ANDROGENS for angina! Even the most stalwart of clinicians is bound to shudder when first confronted with such a seemingly paradoxical concept. Are we to abandon the time-honored therapeutic regimen for angina pectoris —rest, reduction of physical activity to a minimum, avoidance of emotional excitement, and nitroglycerine—in favor of "pep-shots" which have been credited with restoring to the senescent male vigor, energy, and a fresh lust for life? At first sight such an idea would seem fantastic, yet recent reports from several sources suggest that—far from being harmful—injections of testosterone propionate have proved highly beneficial to the stenocardiac.

The first to call attention to the favorable effects of this hormone on vascular disease were Edwards, Hamilton, and Duntley [1] in 1939. By spectrophotometric study they demonstrated that there was a lack of arterial blood supply in the skin of castrated men and that the blood supply to the skin increases after the administration of testosterone propionate to such patients. They also observed improvement in three patients with Buerger's disease and four patients with arteriosclerosis, all of whom had intermittent claudication. Under testosterone therapy the claudication was greatly diminished or abolished and the peripheral blood supply was improved. In 1940 Herrman and McGrath [2] published similar results from estrogenic therapy in vascular spasm due to angiitis of the extremities.

Walker [3] was the first in this country to report beneficial effects of testosterone, as well as of other sex hormones, in cardiac disease. The anginal syndrome was greatly improved with an increase in exercise and emotional tolerance. Marked relief was obtained in 7 of 9 men treated with testosterone propionate and 2 of 3 women treated with estrogens. It was suggested, however, that the psychotherapeutic effect of the injections might have been responsible for some of the apparent improvement. In 1941, Bonnell, Pritchett, and Rardin [4] announced encouraging results in 22 of 23 cases of angina pectoris treated with estrogenic and androgenic substances. They cite experimental evidence to indicate that all sex hormones may have a vasodilating effect on the coronary vessels. Their clinical study was

[1] EDWARDS, E. A., HAMILTON, J. B., and DUNTLEY, S. Q.: Testosterone propionate as a therapeutic agent in patients with organic disease of the peripheral vessels, New England Jr. Med., 1939, ccxx, 865.

[2] HERRMAN, M. D., and MCGRATH, E. J.: The effect of estrogens in vascular spasm due to active angiitis in the extremities, Arch. Surg., 1940, xl, 334.

[3] WALKER, T. C.: (a) The use of testosterone propionate and estrogenic substance in cardiovascular disease: preliminary report, Med. Rec. and Ann., 1940, xxxiv, 667. (b) The use of testosterone propionate and estrogenic substance in the treatment of essential hypertension, angina pectoris, and peripheral vascular disease, Jr. Clin. Endocrinol., 1942, ii, 560–568.

[4] BONNELL, R. W., PRITCHETT, C. P., and RARDIN, T. E.: Treatment of angina pectoris and coronary artery disease with sex hormones, Ohio State Med. Jr., 1941, xxxvii, 554.

inaugurated in 1936 after they had heard that estrogen had been employed by European physicians in the treatment of angina pectoris.

In a preliminary report published in 1942, Lesser [5] described the effects of testosterone propionate in 20 men and 4 women patients in whom the diagnosis of angina pectoris was clearly established. Twenty-five milligrams of the drug (in sesame oil) were administered intramuscularly every second to fifth day for a total of between 5 and 25 injections. Favorable results were obtained in all cases in that the frequency, severity, and duration of attacks were diminished, and the patients were able to increase their physical activities to a considerable degree without precipitating attacks. The beneficial effects of this treatment persisted from 2 to 12 months after treatment was discontinued. The improvement in the men was much greater than in the women. No appreciable improvement was noted following control injections of plain sesame oil. In the majority of patients, there was a lowering of blood pressure during the course of testosterone therapy, the significance of which was regarded as questionable. Fluoroscopic examination, serial kymograms, and electrocardiograms showed no uniform changes that could be attributed to the treatment. No untoward effects were observed in any of the patients studied, although it is to be noted that one patient died of a coincidental coronary thrombosis during treatment and three others died of similar cause within a year after androgenic therapy had been discontinued.

A year later Lesser [6] published further observations on the treatment of angina pectoris with testosterone propionate, adding 22 new patients to bring his total series up to 46 patients successfully treated. Of the more recent group, four patients were studied by means of exercise tolerance tests under standardized conditions before and during the course of therapy, in order to obtain quantitative measurements of their improvement. In each of these patients it was found that the amount of work done before the development of an anginal attack was increased under testosterone therapy and that the severity of the attacks, as measured by the duration of pain, was correspondingly diminished. In each case, subjective improvement was reported before quantitative changes could be demonstrated. Lesser repeatedly stresses the fact that testosterone does not afford immediate relief from an anginal attack as does nitroglycerine. He recommends that in the use of testosterone propionate for the treatment of angina pectoris it is important to individualize each patient on the basis of his response to the drug and to give an adequately long course of therapy. The longest period that any of his patients was free of anginal attacks was 18 months.

[5] LESSER, M. A.: The treatment of angina pectoris with testosterone propionate. Preliminary report, New England Jr. Med., 1942, ccxxvi, 51–54.

[6] LESSER, M. A.: The treatment of angina pectoris with testosterone propionate. Further observations, New England Jr. Med., 1943, ccxxviii, 185–188.

Hamm [7] has claimed similar success in all seven victims of angina pectoris whom he treated with testosterone propionate. He emphasizes the frequent coexistence of the climacteric syndrome and coronary artery disease as adding support to the rationale of androgenic therapy in angina pectoris. More recently Sigler and Tulgan [8] have reported their results in the testosterone treatment of 20 patients with angina pectoris. There was unmistakable evidence of symptomatic relief in 11 cases. Patients who had previously been unable to walk more than one block without the use of nitroglycerine were able to walk many blocks without resorting to the use of this drug. In 5 other cases the response was less spectacular, and in 4 cases no amelioration whatsoever was obtained. Relief from symptoms, when present, continued as long as the testosterone was used, and in some cases persisted for two to four weeks after the injections were discontinued. The symptoms then returned with increasing intensity until they had become as severe as they were before treatment was started. Although symptomatic relief was definite, objectively no changes were observed in the physical or electrocardiographic findings. There was a striking difference in response to testosterone propionate as compared with that to plain sesame oil in a control group of six patients. The authors conclude that, although the number of cases that showed a definite response is relatively smaller in their series, their results were sufficiently encouraging to warrant further trial in a larger number of cases.

The mechanism of action of androgens in coronary artery disease, if such there be, has not been elucidated. True, the androgens and estrogens are both supposed to possess cholinergic and vasodilator properties, based on studies on the skin of experimental animals and castrate human males. To the best of the writer's knowledge, there is no objective proof that these hormones directly influence the coronary blood-flow. It has been suggested that the androgens may promote mental relaxation which in turn would induce vascular relaxation. Even if this were the only effect in angina pectoris, still the results would justify their administration as a therapeutic measure. The practical disadvantages of androgenic therapy are two: the high cost of the androgenic preparations and the inconvenience to the patient of frequent visits to the physician's office for injections. The cost would be justified if such benefits as have been enumerated might be expected. As to the inconvenience to the patient, it seems logical to assume that, if injections of testosterone are truly effective, oral administration of methyl testosterone might well produce similar results. Of course, a potential danger of androgen therapy in angina pectoris is, as Hamm expresses it, "the undesirability of unduly stimulating the libido of such patients." Fortunately or unfortunately, depending on the point of view of the individual

[7] HAMM, L.: Testosterone propionate in the treatment of angina pectoris, Jr. Clin. Endocrinol., 1942, ii, 325–328.

[8] SIGLER, L. H., and TULGAN, J.: Treatment of angina pectoris by testosterone propionate, New York State Jr. Med., 1943, xliii, 1424–1428.

concerned, this libido-stimulating effect is not necessarily manifest in a large proportion of the patients in the age group usually afflicted with angina.

All in all, as one reviews the reports that have been published to date, one cannot but be impressed by the high incidence of beneficial effects that have been claimed for the relatively new androgenic therapy of angina pectoris. However, as many of the authors emphasize, these results must be accepted with the utmost of caution, especially when we recall the many forms of therapy for angina pectoris that have been highly touted in the past, only to fall into obscurity as they failed to survive the test of time. None of the series of cases published to date is very large, and the 100 per cent success attained in certain of these sounds almost too good to be true. Adequate control periods were carried out in only a small proportion of the cases. We must bear in mind that, when one is dealing with a syndrome such as angina pectoris where subjective factors far outweigh objective manifestations, the psychotherapeutic effect of any new form of medication, especially if given by injection, may be tremendous. The clinical differentiation between true angina and pseudo-angina is not always so simple a matter as some would have us believe. It is easy to see how one might be misled by dramatic relief from precordial pain obtained in a tense "climacteric" male whose nervous tension disappeared behind the veil of "well-being" which the androgens are credited with creating. Obviously before any final conclusion can be reached regarding the true value of testosterone propionate in angina pectoris, a series of at least 100 patients should be treated with alternating periods of testosterone therapy and injections of plain sesame oil, using every second case as a control at the start. This study should be carried out in a large cardiac clinic whose members are willing to approach the problem with completely open minds. Such a large-scale project would seem fully justified on the basis of the encouraging preliminary reports, and only in this way will the final answer as to the efficacy of androgens in angina be assured. Meanwhile, no doubt, many sporadic anginal victims will receive injections of testosterone propionate—some with benefit, some with indifferent results, and an occasional one perchance will succumb suddenly a bit before his allotted time while happily plying his oar across the River Styx!

W. H. B.

BOOK REVIEWS

Clinical Laboratory Diagnosis. Second Edition. By SAMUEL A. LEVINSON, M.S., M.D., and ROBERT P. MACFATE, Ch.E., M.S., Ph.D. 980 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1943. Price, $10.00.

The additional material incorporated in the second edition has enhanced the usefulness of this already valuable text. The section on metabolism has been expanded and a discussion of acid base balance and water balance is now included. Bergey's latest nomenclature and classification have been used in the chapter on bacteriology, to which have been added detailed technics for the isolation and identification of bacteria. The chapters on chemistry and hematology have been revised and expanded. The special appendix on the Course in Clinical Pathology at the University of Illinois has been deleted.

This text appears to be one of the more comprehensive of those written for Clinical Pathology and should prove a valuable reference for students, interns, and others interested in laboratory procedures and their interpretation.

M. A. A.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Essentials of Dermatology. Second Edition. By NORMAN TOBIAS, M.D. 497 pages; 20 × 13 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $4.75.

Synopsis of Materia Medica, Toxicology and Pharmacology. Third Edition. 759 pages; 20 × 13 cm. 1944. C. V. Mosby Company, St. Louis. Price, $6.50.

Scabies. By KENNETH MELLANBY, B.A.(Cantab.), Ph.D. 81 pages; 17 × 11 cm. 1943. Oxford University Press, New York. Price, $1.50.

Human Constitution in Clinical Medicine. By GEORGE DRAPER, M.D., C. W. DUPERTUIS, Ph.D., and J. L. CAUGHEY, JR., M.D., Med. Sci. D. 273 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $4.00.

A New Test for Syphilis. By ANSON LEE BROWN, A.B., M.D. 23 pages; 21.5 × 15 cm. 1944. Dr. Brown's Clinical Laboratory, 327 East State Street, Columbus, Ohio. (Taken from Dr. Brown's Third Edition of "Technical Methods for the Technician.")

The Chemistry of Organic Medicinal Products. Second Edition. By GLENN L. JENKINS and WALTER H. HARTUNG. 675 pages; 22 × 14.5 cm. 1943. John Wiley & Sons, Inc., New York. Price, $6.50.

Childbirth without Fear. By GRANTLY DICK READ, M.A., M.D. 259 pages; 21.5 × 14.5 cm. 1944. Harper & Brothers, New York. Price, $2.75.

The Permeability of Natural Membranes. By HUGH DAVSON, D.Sc., and JAMES FREDERIC DANIELLI, D.Sc., A.I.C. With a foreword by E. NEWTON HARVEY. 361 pages; 22 × 14.5 cm. 1944. The Macmillan Company, New York. Price, $4.75.

Office Treatment of the Nose, Throat and Ear. By ABRAHAM R. HOLLENDER, M.Sc., M.D., F.A.C.S. 480 pages; 21 × 14.5 cm. 1943. The Year Book Publishers, Inc., Chicago. Price, $5.00.

Recent Advances in Medicine. Eleventh Edition. By G. E. BEAUMONT, M.A., D.M.(Oxon.), F.R.C.P., D.P.H.(Lond.). 412 pages; 21 × 14. 1943. The Blakiston Company, Philadelphia. Price, $5.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,601 Fellows and Associates of the College on active military duty. Herewith are reported the names of 21 additional members, bringing the grand total to 1,622.

Belford C. Blaine
John D. Call
Russell A. Garman
Benedict R. Harris
Edward H. Hashinger
Joseph Hughes
Byrl R. Kirklin
Julian S. Long
Philip W. Morgan
Howard M. Odel
George P. Perakos
Orman C. Perkins
L. Paul Ralph
E. Burkett Reed
Edward F. Rosenberg
Henry I. Shahon
J. Dunbar Shields, Jr.
Robert A. Ullman
Asher A. White
Stuart Yntema
Ellis W. Young

Major Seale Harris, Jr., (MC), AUS, formerly of Birmingham, Ala., died while on active service at Brisbane, Australia, December 22, 1943.

Captain Lewis T. Stoneburner, III, (MC), AUS, of Richmond, Va., has been reported missing in action (African theater) since Oct. 19, 1943.

Gifts to the College Library

Reprints

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Kenneth L. Burt (Associate), Erie, Pa.—1 reprint;
Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La.—1 reprint;
Dr. Wayne Gordon, F.A.C.P., Billings, Mont.—1 reprint;
Dr. Arthur J. Logie, F.A.C.P., Miami, Fla.—2 reprints;
Dr. Lionel S. Luton, F.A.C.P., St. Louis, Mo.—1 reprint;
Dr. Thomas P. Murdock, F.A.C.P., Meriden, Conn.—11 reprints;
Dr. Lawrence Parsons, F.A.C.P., Reno, Nev.—8 reprints;
Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.—1 reprint;
Michael Peters (Associate), Lieutenant, (MC), AUS—1 reprint;
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—1 reprint;
Dr. R. Kohn Richards (Associate), North Chicago, Ill.—8 reprints;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—2 reprints;
Paul S. Strong (Associate), Captain, (MC), AUS—1 reprint;
Dr. Franklin H. Top (Associate), Detroit, Mich.—7 reprints;
Dr. Harry Warshawsky (Associate), West Lebanon, N. H.—1 reprint.

New Life Members

The following Fellows have become Life Members of the College, bringing the total of new Life Members since January 1, 1944, to fifty-six:

Dr. Herman P. Gunnar, Berwyn, Ill.
Dr. Ramon M. Suarez, Santurce, San Juan, P. R.
Dr. James Howard Agnew, Houston, Tex.
Dr. Richard Edward Knapp, Hackensack, N. J.
Dr. Harry Burger Thomas, York, Pa.

Dr. Francis Roman Wise, York, Pa.
Dr. Julius H. Comroe, Sr., York, Pa.
Dr. Daniel Vincent Conwell, Wichita, Kan.
Dr. Harold Swanberg, Quincy, Ill.
Dr. Roy R. Snowden, Pittsburgh, Pa.
Dr. W. E. R. Schottstaedt, Fresno, Calif.
Dr. Norman Stewart Skinner, St. John, N. B., Can.
Dr. Julian Derwent Loudon, Toronto, Ont., Can.
Dr. Eugene P. Pendergrass, Philadelphia, Pa.
Dr. Lewis Jefferson Moorman, Oklahoma City, Okla.

All Life Membership fees, plus the original initiation fee, are deposited in the permanent Endowment Fund of the College, thus contributing to the perpetuity of the organization. The College plan of Life Membership, based on the age of the Fellow, affords the member an opportunity of paying his full dues during his most productive years and while his income is greatest, thus avoiding the burden of dues later in life. It offers the premium of fully active Fellowship for life, instead of merely to the age of sixty-five.

According to a survey of the U. S. Department of Commerce in 1942, physicians' highest average net income ($7,097.00) is reached between the ages of 50 to 54, with a rather marked decline thereafter ($5,294.00 for ages 55 to 59; $4,574.00 for ages 60 to 64; $2,552.00 for ages 65 and over). The most appropriate ages during which members could best afford Life Membership are from 40 to 54. Add to this consideration the fact that physicians' incomes are much higher at present than may be reasonably anticipated in the postwar era, that federal taxes are high at present, but Life Member subscriptions are deductible.

Schedule of Examinations by Certifying Boards

American Board of Internal Medicine:
William A. Werrell, M.D., Assistant Secretary-Treasurer
1301 University Ave.
Madison, Wis.

Written Examination: October 16, 1944. To be held in various centers throughout the United States. Candidates in the Military and Naval Services may take the written examination at their stations, with the permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service regardless of the closing date for the acceptance of applications.

Oral Examination: Chicago, Ill., March 30–31, 1944. Number of candidates restricted; applications will be considered in order of receipt; closing date, March 20. Communicate with the Assistant Secretary-Treasurer concerning succeeding oral examination.

American Board of Dermatology and Syphilology:
C. Guy Lane, M.D., Secretary
416 Marlboro St.
Boston, Mass.

Written Examination: Various large cities, May 8, 1944. Applications must be filed by April 1, 1944.

Oral Examination: Chicago, Ill., June 9–10, 1944. Applications must be filed by April 15, 1944.

AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 115½ First Ave., S.W. Rochester, Minn.	*Written Examination:* September 22, 1944. Locally under monitors. *Oral Examination:* St. Louis, Mo., November 8–9, 1944. Preceding annual meeting of the American Academy of Pediatrics and the Southern Medical Association. Applications for admission to these examinations must be filed not later than July 8, 1944.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N.W. Washington, D.C.	*Written Examination:* March 31, 1944. In various cities; applications closed March 1. *Oral Examination:* Philadelphia, Pa., May 12–13, 1944.
AMERICAN BOARD OF RADIOLOGY: B. R. Kirklin, M.D., Secretary Mayo Clinic Rochester, Minn.	This Board conducts only a general oral examination. The last examination was held at Chicago, February 14–15–16, 1944. The time and place of the next examination, some time in the autumn of 1944, will be announced later.

THE CHARLES MAYER FELLOWSHIPS

The Committee on Medical Education of The New York Academy of Medicine has awarded three of the four Fellowships provided by Dr. Charles Mayer to Dr. Harry Goldblatt, F.A.C.P., of Western Reserve University, to the Cancer Research Laboratory of The Mount Sinai Hospital, New York City, and to Dr. John R. Murlin of the University of Rochester, New York.

A fourth Fellowship of $2,000 for research on the "Study of the Relationship between Precancerous Lesions of the Mouth, Hepatic Insufficiency and Gastrointestinal Disorders" will be held open for further applications until April 15, 1944.

Applications should be sent to Dr. Mahlon Ashford, Secretary of the Committee, 2 E. 103d St., New York City, not later than April 1, 1944.

AMERICAN PHYSICIANS' ART ASSOCIATION

will have its seventh annual exhibit at the A.M.A. convention, Stevens Hotel, Chicago, June 12–16, 1944.

Through the courtesy of Mead Johnson & Co., Evansville, Ind., there will be no fees for hanging and no express charges either way. The type of art to be exhibited includes personal work of the following types of medium: oil portraits, oil still life, landscapes, sculpture, water color, pastels, etchings, photography, wood carving, leather tooling, ceramics and tapestries (needle work). All pieces should be sent preferably by railway express collect, automatically covered with $50 insurance.

Exhibitors should send NOW for entry blanks to Dr. Francis H. Redewill, Secretary, A.P.A.A., Flood Building, San Francisco.

There will be about 100 trophies, including medals and plaques.

Three prominent Fellows of the American College of Physicians returned to this country in December as passengers on the *Gripsholm* after considerable terms in Japanese Concentration Camps in China.

Dr. William W. Cadbury, F.A.C.P., served for many years as Superintendent of the Canton Hospital and Professor of Internal Medicine at Sun Yat Sen Medical

College of Lingnan University, and Chairman of the Canton International Red Cross. Dr. Cadbury's temporary address is 260 E. Main St., Moorestown, Burlington County, N. J.

Dr. Josephine C. Lawney, F.A.C.P., was Dean and Professor of Medicine at the Woman's Christian Medical College and Chief of Medical Service at the Margaret Williamson Hospital in Shanghai. Dr. Lawney's temporary address is Prince George Hotel, 14 E. 28th St., New York 16, N. Y.

Dr. Frederick G. Scovel, F.A.C.P., was Superintendent and Director of Medical Service at the Bachman-Hunter Hospital, Tsining, Shantung, China. Dr. Scovel's present address is 164 Brunswick St., Rochester, N. Y.

Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, was appointed Surgeon General of the Military Order of the World Wars at its Cincinnati convention recently. This is a patriotic organization whose membership consists of commissioned officers of both World Wars.

The Fortieth Annual Congress on Medical Education and Licensure was held in Chicago, February 14–15, 1944. The following Fellows participated in the program:

Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C.—"Readjustments of Returning Medical Officers";

Major General George F. Lull, F.A.C.P., Washington, D. C.—"The Army Medical Officer in Action";

Rear Admiral Ross T. McIntire, F.A.C.P., Washington, D. C.—"Medicine in the Navy";

Dr. Thomas Parran, F.A.C.P., Washington, D. C.—"The Expanding Field of Public Health";

Captain Edward L. Bortz, F.A.C.P., Philadelphia, Pa.—"War-Time Graduate Training";

Dr. Frank M. Fuller, F.A.C.P., Keokuk, Iowa—"Annual Report of The Federation of State Medical Boards of the United States";

Dr. Jean A. Curran, F.A.C.P., Brooklyn, N. Y.—"Hospital Internship";

Dr. George W. Covey, F.A.C.P., Lincoln, Nebr.—"The Amended Nebraska Medical Practice Act."

Dr. Anton J. Carlson, F.A.C.P., Chicago, was recently made President of the American Association for the Advancement of Science.

Commander Edward L. Bortz, (MC), U. S. Naval Reserve, Philadelphia, was recently promoted to the rank of Captain.

Dr. Kenneth M. Lynch, F.A.C.P., has succeeded Dr. Robert Wilson, F.A.C.P., as Dean of the Medical College of the State of South Carolina, his duties having started at the conclusion of the past academic year. For several years Dr. Lynch has been a member of the Board of Governors of the American College of Physicians, a member of the Board of Directors of the American Society for the Control of Cancer, Chairman of the South Carolina Cancer Commission and Chairman of the South Carolina State Board of Health. He has been the recipient of the Gold Medal of the American Medical Association and of the Research Medal of the Southern Medical Association. In 1930 the University of South Carolina conferred upon him the honorary degree of Doctor of Laws.

Lieutenant Colonel Lee Rice, (MC), AUS, San Antonio, Tex., is Consultant to the Veterans Administration Facility at Hines, Ill. This hospital has a tumor clinic of 500 beds.

Captain Lewis T. Stoneburner, III, (MC), AUS (Associate), Richmond, Va., is reported missing in action in the African theater since October 10, 1943. He was connected with the General Hospital that was formed in Richmond. He was Chief Consultant in Medicine for the North African theater and assigned to visit various hospital units and report on conditions to his commanding officer. Although no details of his disappearance have been announced, it is thought that his plane was shot down on one of his inspection trips.

The American Hospital Association is directing a Postwar Planning Committee to study postwar hospitalization needs of America. The Kellogg Foundation made a grant of $35,000 and the Commonwealth Fund a grant of $15,000 for the two-year program.

For the second time, Dr. Walter Freeman, F.A.C.P., Professor of Neurology, George Washington University School of Medicine, Washington, D. C., has delivered the Davidson Lecture before the Medical Society of the District of Columbia. His recent presentation was entitled, "Frontiers of Multiple Sclerosis."

Dr. Chauncey C. Maher, F.A.C.P., Chicago, on March 8 delivered a lecture on "Chronic Disease and Its Implications as a Social Problem" in a series of lectures on medical care at the University of Illinois College of Medicine.

Dr. Robert L. Levy, F.A.C.P., New York City, and Dr. Walter L. Palmer, F.A.C.P., Chicago, gave the sections on cardiology and gastroenterology, respectively, before the 8th Annual Session of the New Orleans Graduate Medical Assembly, March 6–9.

Dr. Louis Hamman, F.A.C.P., Baltimore, on February 7 gave a paper on "The Place of Psychiatry in the Teaching of Clinical Medicine" in connection with a symposium on medical education in relation to the practice of medicine of the future at New York University College of Medicine.

Among recent promotions on the faculty at the Long Island College of Medicine, Brooklyn, were:

Dr. George E. Anderson, F.A.C.P., advanced to Clinical Professor of Medicine;
Dr. Arthur E. Lamb, F.A.C.P., advanced to Assistant Professor of Clinical Medicine;
Dr. Edwin P. Maynard, Jr., F.A.C.P., advanced to Professor of Clinical Medicine.

Dr. George T. Harding, III, F.A.C.P., Columbus, Ohio, has been appointed by Governor John W. Bricker a member of a committee to study conditions and needs in all state mental institutions, to make recommendations regarding them to the Governor and to the State Department of Public Welfare.

Dr. Malcolm T. MacEachern, F.A.C.P., and Dr. Henry C. Sweany, F.A.C.P., of Chicago, have been recently appointed as Associate Professors of Medicine at Northwestern University Medical School.

The Boston Dispensary is offering six Fellowships in medicine to clinics and domiciliary medical service for appointments immediately or by July 1. These Fellowships have been approved by the American Board of Internal Medicine in satisfaction of graduate training. Additional information may be obtained from the Director of the Boston Dispensary, 25 Bennet St., Boston.

Dr. Bayard T. Horton, F.A.C.P., Rochester, was elected President of the Minnesota Society of Internal Medicine at its recent meeting.

Dr. Walter P. Gardner, F.A.C.P., Anoka, Minn., is now President of the Minnesota Society of Neurology and Psychiatry.

Dr. James E. Paullin, F.A.C.P., President of the College, made a radio broadcast, February 19, on "Hometown Heroes." This was a part of a series of broadcasts of "Doctors at War" sponsored by the American Medical Association in coöperation with the National Broadcasting Company and the Medical Departments of the United States Army and Navy.

"Health Is on the March" is the title of a series of short wave radio broadcasts inaugurated by the Office of War Information to overseas audiences. Dr. Thomas Parran, F.A.C.P., Washington, Surgeon General of the U. S. Public Health Service, was the first speaker. Dr. Herbert R. Edwards, F.A.C.P., New York City, Director of the Bureau of Tuberculosis, New York City Department of Health, and Dr. James E. Paullin of Atlanta, Ga., President of the College and of the American Medical Association, will be featured on future programs.

On behalf of the National Tuberculosis Association, Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla., President, presented to Yale University on February 3 a permanent collection of 300 chemical compounds isolated from the tubercle bacillus, "material found nowhere else in the history of man" according to Dr. William Charles White, Washington, D. C., Chairman of the Committee on Medical Research of the Association.

Dr. Russell L. Haden, F.A.C.P., Cleveland, will deliver the third Edwin R. Kretschmer Memorial Lecture at the Palmer House, Chicago, on April 28, his subject to be, "The Varying Clinical Picture of Leukemia."

Dr. Alfred W. Harris (Associate), Dallas, Tex., was recently elected President of the Southern Section of the American Federation for Clinical Research.

Dr. Lyell C. Kinney, F.A.C.P., San Diego, Calif., was recently elected President-Elect of the American Roentgen Ray Society.

Dr. George K. Wharton, F.A.C.P., London, Ont., has been appointed Professor of Clinical Medicine at Queen's University, Kingston. Among other degrees held by him is Master of Science in medicine from the Mayo Foundation of the University of Minnesota.

Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn., presented a paper on "Clinical Experience with Antibiotic Agents" in connection with a symposium on this subject conducted by the Chicago Section of the American Chemical Society, at Chicago on February 24.

At a meeting of the New York Diabetes Association at the New York Academy of Medicine, February 19, Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, delivered a "Report on the Philadelphia Diabetes Survey" and Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, gave an address on "Normal Standards in the Treatment of Young Diabetics." Among other speakers were Drs. Seale Harris, F.A.C.P., Birmingham, Ala.; Cecil Striker, F.A.C.P., Cincinnati; Edward S. Dillon, F.A.C.P., Philadelphia; Howard F. Root, F.A.C.P., Boston; and Elliott P. Joslin, F.A.C.P., Boston.

War-Time Graduate Medical Meetings

Future Schedule

Region No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen

Region No. 2 (Connecticut, Rhode Island)—Dr. S. C. Harvey, Chairman; Dr. C. Barker, Dr. A. M. Burgess

Dispensary, U. S. Naval Air Station, Brunswick, Maine

March 16—Symposium on Physiotherapy—Speakers to be announced

Station Hospital, Fort Williams, Portland, Maine

March 16—Head, Spine and Nerve Injuries—Speakers to be announced

Station Hospital, Presque Isle, Maine

March 16—Blood Dyscrasias and Transfusions—Dr. Charles S. Davidson

Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine

March 16—Head, Spine and Nerve Injuries—Speakers to be announced

Station Hospital, Grenier Field, Manchester, New Hampshire

March 15—Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases—Speakers to be announced

U. S. Naval Hospital, Portsmouth, New Hampshire

March 16—Peripheral Vascular Disease—Dr. Richard H. Wallace

Station Hospital, Fort Banks, Boston, Massachusetts

March 16—Fractures of Extremities—Speakers to be announced

U. S. Naval Hospital, Chelsea, Massachusetts

March 16—The Pneumonias and Other Respiratory Infections—Dr. Maxwell Finland

Station Hospital, Fort Devens, Massachusetts

March 16—Chest and Abdominal Injuries—Speakers to be announced

Station Hospital, Camp Edwards, Massachusetts

March 16—Contagious Diseases and Complications—Speakers to be announced

Cushing General Hospital, Framingham, Massachusetts

March 16—Stomach, Biliary Tract, Intestinal Disorders—Drs. Merrill C. Sosman, Simeon B. Wolbach, Francis C. Newton, E. Stanley Emery

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

March 16—Burns and Reconstruction Surgery—Drs. Joseph H. Shortell, Francis Taylor, V. H. Kazanjian

U. S. Marine Hospital, Brighton, Massachusetts

March 16—Acute Abdominal Emergencies—Speakers to be announced

Station Hospital, Westover Field, Chicopee Falls, Massachusetts

March 16—The Skin—Speakers to be announced

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

March 16—The Use of Penicillin and the Sulfa Drugs—Speakers to be announced

U. S. Naval Hospital, Newport, Rhode Island

March 16—Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases—Speakers to be announced

Air Corps Station Hospital, New Haven, Connecticut

March 16—Acute Infections of the Central Nervous System—Dr. Henry R. Viets

New London, Connecticut (U. S. Coast Guard)

March 16—Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation—Drs. Paul D. White, Mandel E. Cohen

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Joliffe, Dr. H. W. Cave

Station Hospital, Fort Niagra, New York

March 15—Neurotropic Virus Disease—Dr. David K. Miller
March 22—Fractures of Short Bones—Speakers to be announced
March 29—Gastric and Duodenal Ulcer—Speakers to be announced
April 5—Knee Disabilities—Dr. Pio Blanco
April 12—Acute Anterior Poliomyelitis—Dr. Francis Gustina

Halloran General Hospital, Staten Island, New York

April 11—Low Back Pain—Dr. Philip D. Wilson

Camp Shanks, Orangeburg, New York

March 16—Treatment of Ano Rectal Diseases in the Army—Dr. Frank C. Yeomans
March 23—Hypertension—Dr. Herbert Chasis
March 30—Fractures—Dr. Clay Ray Murray
April 6—Surgical Bacteriology in the Treatment of Surgical Infections—Dr. Frank L. Meleney
April 13—Present Status of Use of Sulfonamides in Surgery and Medicine—Dr. Walsh McDermott

Grand Central Palace, 480 Lexington Avenue, New York City, New York

March 17—Common Skin Diseases in Soldiers—Dr. George C. Andrews
(To be repeated March 24)
March 31—Peripheral Vascular Disease—Dr. A. Wilbur Duryee
(To be repeated April 7)
April 14—General Surgical Approach to the Abdomen—Dr. John F. Erdmann

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Lieutenant Commander G. C. Griffith, Chairman; Dr. J. S. Rodman, Dr. B. P. Widmann

England General Hospital, Atlantic City, New Jersey

March 21—Low Back Pain—Dr. Paul C. Colonna
April 4—Dysentery—Dr. William D. Sawitz

Station Hospital, Camp Kilmer, New Jersey

March 27—Management of the Anesthesia Period—Dr. Frederick P. Haugen, Lieutenant Commander Don Hale

U. S. Naval Hospital, Philadelphia, Pennsylvania

March 17—Physical Therapy—Lieutenant Commander Jacob L. Rudd
March 31—Psychosomatic Aspects of Cardiovascular Disease—Dr. Edward Weiss, Lieutenant M. M. Pearson

Indiantown Gap, Pennsylvania

March 15—Management of the Anesthesia Period—Dr. Frederick P. Haugen
March 22—Anesthesia—Dr. Henry S. Ruth
A. Spinal Anesthesia
B. Intravenous Pentothal
March 29—Treatment of Syphilis—Dr. Francis G. Harrison

Fort Monmouth, New Jersey

March 15—Treatment of War Wounded in Naval Hospital
Physiotherapy Department—Lieutenant Commander Jacob L. Rudd
Short Wave Diathermy Treatment—Dr. William H. Schmidt
Ultra Violet Therapy—Dr. A. A. Martucci
March 22—Treatment of War Wounded in Naval Hospital
Physiotherapy Department—Lieutenant Commander Jacob L. Rudd
Posture, Physical Exercise and Massage—Dr. Leonard D. Frescoln
March 29—Diabetic Complications—Dr. Joseph T. Beardwood, Jr.

Minutes

Post War Planning Committee Meeting

Joint Committee
of
American Medical Association
American College of Physicians
American College of Surgeons

Meeting held at Hotel Statler, Washington
January 14, 1944

Members of the Committee present were: Dr. Arthur W. Allen, Dr. Francis G. Blake, Comdr. Edward L. Bortz, Dr. Frederick A. Coller, Capt. W. E. Eaton, Dr. Morris Fishbein, Dr. Alan Gregg, Dr. Charles M. Griffith, Dr. Roger I. Lee, Dr. Walter W. Palmer, Dr. James E. Paullin, Dr. G. Morris Piersol, Brig. Gen. Fred Rankin, Dr. H. H. Shoulders, and Dr. Olin West.

The minutes of the meeting of October 15, 1943 were approved as published in the *Journal of the American Medical Association,* October 30, 1943.

Reports of Subcommittees:

Committee on Location and Re-location of Physicians on return from the Service. Dr. Gregg, Chairman, Dr. Allen and Dr. Piersol.

While the Committee appreciated the impossibility of predicting the magnitude of the problem it was their belief that many men in the grades of Lieutenant, Captain and Major would appreciate information about likely places to practice and a certain number will desire communities offering greater possibilities both financial and cultural than those in which they practiced before entering military service. The need of anchor salaries for a period of three to six months seems inevitable. The part that commercial agencies will probably take in the location problem was discussed. All agreed that the American Medical Association could not furnish the type of information supplied by commercial agencies, such as financial arrangements, type of physician required by the individual community and numerous other details without the accusations of being undemocratic. As a result of the deliberations the committee voted to request the Trustees of the American Medical Association to consider the establishment of a bureau of information to aid and supplement the activities of commercial agencies in the location of physicians on their return to active practice. This bureau if established would also have on file information about additional training.

Committee on Interns, Residents and Special Training. Dr. Palmer, Chairman, Dr. Blake and Dr. Coller.

Up to date the work of the Committee had been more or less exploratory. The first and an important consideration was that many different committees throughout the country are "planning" in this field: Individual hospitals, medical schools, county and state societies as well as the American Medical Association, special societies particularly the National Specialty Societies, and to these should be added the Council on Medical Education and Hospitals and the Association of American Medical Colleges. The need of coördination, avoidance of duplication and confusion is great. The best method of coping with the problem seemed to be through establishing a close relation with the Council on Medical Education and Hospitals of the American Medical Association.

The Chairman reported that he had written to twelve of his friends at the head of the medical clinics in teaching hospitals for information concerning any plans under consideration. All were in agreement that enlarged facilities would be needed to continue the training of those men who were unable to finish a reasonably normal intern and resident period before entering military service. In general hospitals

should provide for their own men. Should large numbers of men who had their internships in the smaller non-teaching hospitals make a drive on the teaching hospitals the situation is likely to become hopeless. Probably relatively few men will desire or need more time to complete their internships. Many will have had experience in hospitals which to a large extent will make up for any lack before service. In any event, the number of interns has been reduced in the individual hospitals at the insistence of the Procurement and Assignment Service. The expansion back to the old number can be made by taking on those returning who wish for more training as interns. It is anticipated that the greatest demand will be in the resident and special training groups. There is general agreement among the medical men thus far canvassed that enlarging the resident staff, making greater use of the out patients' departments, the addition of extern residents and a certain sharing of the opportunities between the recently graduated interns and men returning from service will be about the best that can be offered. Also the use of fellowships to a limited extent will provide the necessary training. Obviously any such program will require subsidy. One of the large foundations has already made a handsome contribution to the postwar training problem. It is hoped that others will follow the example.

In Surgery, Dr. Coller has appointed a special committee of the American Surgical Society to study, report and make recommendations on ways and means of meeting the postwar situation in surgery.

So far as the specialties are concerned, most hospitals have had their resident staffs depleted and not only will there be places but men will be eagerly sought. More information about this phase of the problem will be forthcoming at a later date.

Committee on Collection of Information Concerning Postwar Needs. Dr. Abell, Chairman, Dr. Fishbein and Dr. West.

Dr. Fishbein made the report in the absence of the Chairman. A questionnaire to be sent to a 3,000 sample was submitted for discussion and criticism. The questionnaire covers medical school, age, character of training after graduation, practice or salaried position. The questions cover the amount and type of training desired after leaving the service and includes plans as to kind of career contemplated, i.e., academic, general practice, industrial medicine, and the several governmental services.

No items were discussed other than those included in the Committee reports.

Respectfully submitted,

(Signed) CHAIRMAN, A.C.P. COMMITTEE

Dr. George Morris Piersol, F.A.C.P., Secretary General of the American College of Physicians and Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, has been appointed Director of the new Center for Research and Instruction in Physical Medicine in the Graduate School of Medicine of the University of Pennsylvania. He will relinquish his private practice to direct the Center, one of whose objectives is to explore thoroughly the possibilities of physical means of treatment, not only of infantile paralysis but of other diseases as well. To establish this Center, the National Foundation for Infantile Paralysis recently made a grant totaling $150,000.00 for a five-year period from January 1, of this year.

An alumnus of the College of Arts and Sciences and of the School of Medicine of the University of Pennsylvania, Dr. Piersol joined the medical faculty at the University in 1907, and is now Professor of Medicine and Vice-Dean in the Graduate School of Medicine, as well as Professor of Clinical Medicine in the School of Medicine. He is Visiting Physician at the Graduate Hospital of the University and Chief of Staff of that Hospital, active Consultant in Medicine to the Philadelphia General Hospital, Medical Director of the Bell Telephone Company of Philadelphia, and former Director of Medical Services of the Abington Memorial Hospital.

Dr. Piersol is also Editor-in-Chief of the *Cyclopedia of Medicine, Surgery and the Specialties,* Editor of *Clinics,* and has contributed many articles to medical journals and various textbooks.

In addition to being a past President of the American College of Physicians, and its Secretary General for many years, he is a Fellow of the College of Physicians of Philadelphia, a past President of the Philadelphia County Medical Society, the American Gastro-enterological Association and the American Clinical and Climatological Association.

During the First World War, Dr. Piersol was a lieutenant colonel and served for a time as commanding officer of Base Hospital No. 20, University of Pennsylvania Medical Unit. Later he became Medical Consultant to the Fourth Army of the A.E.F. He has been on the Medical Council of the Veterans Administration for many years.

Establishment of The Passano Foundation, Incorporated, is announced by The Williams & Wilkins Company. The purpose of the Foundation as set forth in its charter is: "For scientific and educational purposes, particularly to provide for scientific research and to publish the results of scientific research and to make awards for meritorious achievements in scientific research."

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School, is a director of the Foundation. Dr. George Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington, is also a director. Mr. Robert S. Gill, President of The Williams & Wilkins Company, has been elected President of the Foundation and Mr. George Hart Rowe, of The Williams & Wilkins Company, is a director. Headquarters are at Mt. Royal and Guilford Avenues, Baltimore 2, Maryland.

Mr. E. B. Passano, for whom the Foundation is named, is Chairman of the Board of The Williams & Wilkins Company. He has been actively identified with the development of scientific publishing over a period of more than 35 years.

By the terms of the charter of the Foundation, the Board of Directors may inaugurate the establishment of an annual award not to exceed $5,000 for the outstanding contribution to the advancement of medical science made within the year by an American citizen.

A number of other projects are under consideration. One is the advancement of post-graduate instruction among physicians in sections of the country not accessible to medical centers in the larger cities.

As indicated, the declared purpose of the Foundation is broad and consideration will be given to any activity within its limits.

OBITUARIES

DR. LEWELLYS FRANKLIN BARKER

On July 13, 1943, Baltimore lost one of its outstanding nationally known internists in the death of Dr. Lewellys Franklin Barker.

Dr. Barker was born September 16, 1867, in Norwich, Ontario, Canada. He graduated from the Toronto Faculty of Medicine and did postgraduate study in Leipzig, Munich and Berlin. He became professor of medicine at Johns Hopkins University and Chief Physician at the Hospital in 1905 and remained so until 1913, after which he became emeritus professor of medicine and visiting physician, respectively. His publications were voluminous. His contacts and positions held in medical societies were too numerous to mention.

Dr. Barker was not only one of Baltimore's outstanding physicians, but of the Country as well,—one might say without hesitation, internationally known. He received many honorary degrees and his lectures were given from one end of the Country to the other. With all of his many interests, one must not forget that Dr. Barker had a very important hand in the reorganization of this College in 1926 and, as far as Baltimore and Maryland were concerned, was always a loyal supporter of all interests of the College. Dr. Barker was a man of strong personality whose interests extended beyond those of medical societies into all the aspects of the community, both scientific and social. Only a man of tremendous energy, as well as ability, could accomplish so much.

It is with deepest sympathy that we extend our condolences to his family and many friends.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

MAJOR SEALE HARRIS, JR.

Major Seale Harris, Jr., of Birmingham, Alabama, was born at Union Springs, Alabama, October 9, 1900, and died of heart disease while in the service of his country in Brisbane, Australia, December 22, 1943. Major Harris received his B.S. in 1924 at the University of Alabama, his M.D. at Johns Hopkins University School of Medicine in 1926. He was an Intern in the Baltimore City Hospitals in 1926–27, and Resident in Medicine, Gorgas Hospital, Panama, in 1927–28. For several years he was Assistant Professor of Medicine at Vanderbilt University School of Medicine. Since 1936 he had been Visiting Physician at Highland Baptist Hospital, and since 1939 at Hillman Hospital. He was former Vice President, Chattahoochee Valley Medical Society, former Secretary and former Treasurer, Birmingham Clinical Club. He was a member of the Southern Interurban Clinical Club, Southern Medical Association, Medical Association of the State of Alabama, American Heart Association, Fellow of the American Medical

Association, and since 1939, Fellow of the American College of Physicians. He was the author of many published medical papers.

In January, 1942, he entered active duty with the Medical Corps of the United States Army and for seven months was head of an army base hospital in the Fiji Islands, and later, second in command of an army base hospital in Brisbane, Australia, where he died at the youthful age of 43.

Major Harris was of distinguished medical lineage and himself was a brilliant young man. He was esteemed highly by the profession of the State for his knowledge of medicine and his ability as a physician, and was greatly loved by both physicians and laity for his fine personal traits. His death at such an early age brings to an end a career of great promise.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DR. JAMES ALTO WARD

Dr. James Alto Ward, while on a fishing trip at Inland Lake near Birmingham, died November 11, 1943, when his boat accidentally overturned. A friend who was with Dr. Ward lost his life in the same accident. Dr. Ward was born at Hartford, Alabama, April 6, 1892, received his A.B. degree at Howard College, Birmingham, 1914, and his M.D. at Johns Hopkins University School of Medicine, 1918. He was an Intern at Johns Hopkins Hospital during the year 1918–19, and an Extern in 1919–20, and Resident Physician, Bon Secour Hospital, in 1919–20. In 1924 he became Professor of Clinical Microscopy at Howard College, which position he held until 1931. He was formerly Visiting Physician to the Hillman Hospital and University Dispensary and for many years Visiting Physician, Birmingham Baptist Hospital. Dr. Ward was a member of the Jefferson County Medical Society, Medical Association of the State of Alabama, Southern Medical Association, and American Medical Association. Since 1935 he had been a Fellow of the American College of Physicians.

Dr. Ward was a keen student of medicine, the author of many published medical papers and had a very extensive practice. He was always interested in the advancement of our profession, was an upstanding, patriotic citizen, and was greatly beloved by a large circle of patients and friends. His tragic death brought an untimely end to the career of one of the leading medical figures of Alabama.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DR. JOHN LANAHAN DORSEY

On September 15, 1943, Dr. John Lanahan Dorsey, widely known practitioner of Baltimore, died in the Johns Hopkins Hospital, following an operation for brain tumor.

Dr. Dorsey had been ill for some months and only recently his illness reached an acute stage. Dr. Dorsey was born in Baltimore December 14, 1893, graduating from the Johns Hopkins University in 1914 and the Medical School in 1918. Since his graduation Dr. Dorsey had devoted most of his time to the general practice of medicine. He was instructor in Medicine in Johns Hopkins School of Medicine, Assisting Visiting Physician at Johns Hopkins Hospital, a member of the local Medical Societies, Fellow of the American College of Physicians since 1930 and a diplomate of the American Board of Internal Medicine.

Dr. Dorsey enjoyed an enviable reputation and an unusually large practice, and his loss is an irreparable one for his host of friends and associates. Such a tragic ending for a man so young and valuable is hard to understand.

Dr. Dorsey had better opportunities than most physicians to sit in his office to select not only his type of practice but also his patients. He chose instead the harder life and he lived it with full conscientiousness. Like Chaucer's parson—neither rain nor thunder prevented him from visiting the great or the small who needed him. His loss will always be keenly felt and his place in the profession hard to fill.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland